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COCCIDIOIDOMYCOSIS

Persistence of Residual Pulmonary Lesions

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AND

R. BERKE, M.D.

NEW YORK

NUMEROUS former military personnel of World War II (actual figures not available) have served in the southwestern desert area of this country, where coccidioidomycosis is endemic. The presence of these troops in large numbers has stimulated study of the disease. It is now known that about 80 per cent of the long time residents of the endemic area are infected and that about 25 per cent of the military personnel with several months' residence in the endemic area became infected.[1] From 20 to 25 per cent of infections are clinically recognizable.[2]

It is not the purpose of this paper to present a detailed discussion of such factors as the etiologic agent (the fungus Coccidioides immitis) and its life cycle, the pathogenesis or racial differences in incidence. These and other fundamental data have already been described amply in the literature. The primary purpose is to present data on a series of patients residing in New York city with protracted residual pulmonary lesions of coccidioidomycosis and to discuss the pitfalls in diagnosis. Although it has been estimated [3] that roentgenoscopy shows

From the Thoracic Unit, New York Regional Office, Veterans Administration.

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1. Smith, C. E.; Beard, R. R.; Rosenberger, H. G., and Whiting, E. G.: Effect of Season and Dust Control on Coccidioidomycosis, J.A.M.A. **132**:833 (Dec. 7) 1946.

2. Smith, C. E.; Beard, R. R.; Whiting, E. G., and Rosenberger, H. G.: Varieties of Coccidioidal Infection in Relation to Epidemiology and Control of Diseases, Am. J. Pub. Health **36**:1394 (Dec.) 1946.

3. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1945, p. 55.

pulmonary changes in 80 per cent of cases, no follow-up study of these changes in cases outside the endemic area has been reported previously.

One of us (H. E. B.) [4] reported on a group of cases with pulmonary lesions, but these observations were limited to relatively recent infections. The case reports which follow constitute a two to five year follow-up study of various residual lesions of coccidioidomycosis. The patients forming the basis for this report were veterans of World War II who had returned to civilian life in New York city. In the majority of instances the diagnosis of pulmonary coccidioidomycosis

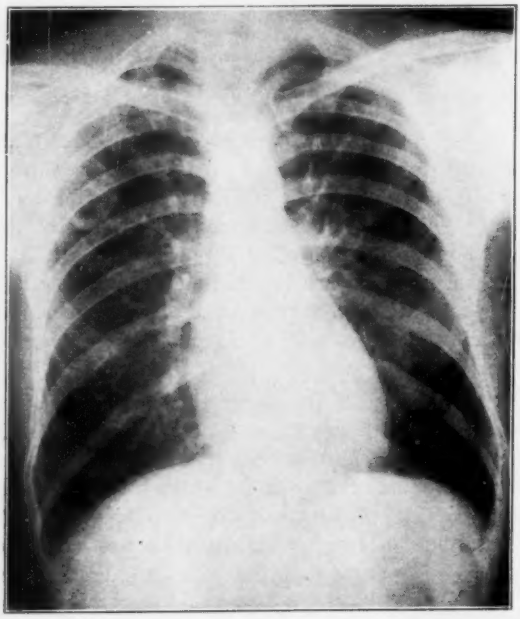

Fig. 1.—Solitary large cavity, with fluid level, in upper part of right lung field.

had been made prior to discharge from military service. In several instances no definite diagnosis had been made. In some of the cases the condition had subsequently been diagnosed as tuberculosis or other pulmonary diseases. Twenty cases with various types of pulmonary residual lesions were encountered in this series. The importance of diagnosis, particularly of differentiation from pulmonary tuberculosis, will be emphasized in the case reports and in the discussion which follows. Thirteen of the more representative cases will be described.

4. Bass, H. E.; Kooperstein, S. I.; Friedman, M. M., and Kastlin, G. H.: Pulmonary Coccidioidomycosis, Dis. of Chest **12**:371 (Sept.-Oct.) 1946.

REPORT OF CASES

CASE 1.—Solitary large cavity. A routine roentgenogram of the chest made at the time of discharge from the Army, in December 1945, showed a cavity in the right lung. The patient was asymptomatic. There was a history of contact with a tuberculous brother prior to induction, and the initial diagnosis was tuberculosis. Further history revealed six months' exposure in the California-Arizona desert in 1942. Specimens of sputum were negative for tubercle bacilli and fungi. Reactions to tuberculin tests were negative in all dilutions. The coccidioidin skin test gave a positive reaction in a dilution of 1:1,000. The serologic reactions were negative. The final diagnosis was coccidioidal cavity in the lung. A roentgenogram of the

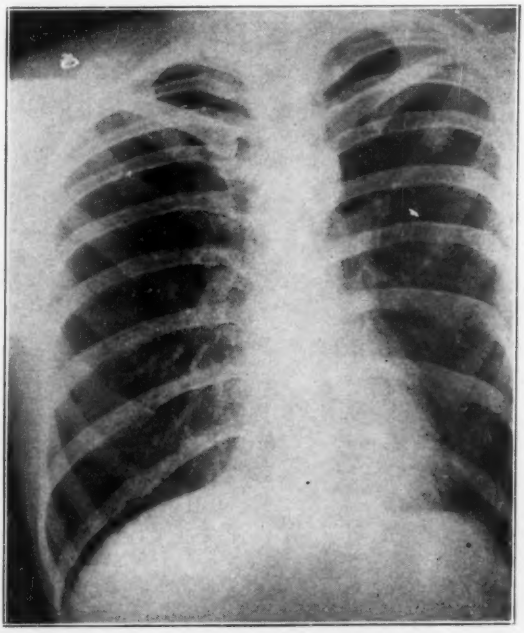

Fig. 2.—Single round area of density at left second rib anteriorly.

chest on Sept. 17, 1947 (fig. 1) showed a large cavity, 5 by 4 cm., with a fluid level, in the upper part of the right lung. The cavity has not shown any change in two years of observation. The rest of the lung fields is normal.

CASE 2.—Solitary round area of density. The patient, a laboratory technician, had handled cultures from patients with coccidioidomycosis in an endemic area in Arizona. A routine roentgenogram of the chest made at a separation center in May 1946 showed a round area of density in the upper lobe of the left lung. The patient was asymptomatic. Reactions to both coccidioidin and tuberculin skin tests were positive. A roentgenogram of the chest taken on Oct. 16, 1946 (fig. 2) showed a round area of density, measuring 2 cm., at the left second rib anteriorly. A follow-up roentgenogram of the chest taken at the time of this report two years later, indicates no change in the area of density.

CASE 3.—Small irregular area of density. The patient underwent desert training in the California-Arizona maneuver area in 1942 and 1943. In August 1943 he experienced a sudden episode of weakness and pain in the chest. A roentgenogram of the chest showed bilateral pulmonary infiltrations and an increase in hilar density in the left lung. Reactions to both coccidioidin and tuberculin skin tests were positive. A roentgenogram of the chest taken on Oct. 1, 1946 indicated a small, irregular area of density at the left first interspace anteriorly. A follow-up roentgenogram shows no change in the lesion in two years; the reaction to the skin test with coccidioidin remains positive.

CASE 4.—Stationary apical cavity. The patient, a 28 year old Negro, had been exposed to desert conditions near Phoenix, Ariz., from August 1942 to May 1943.

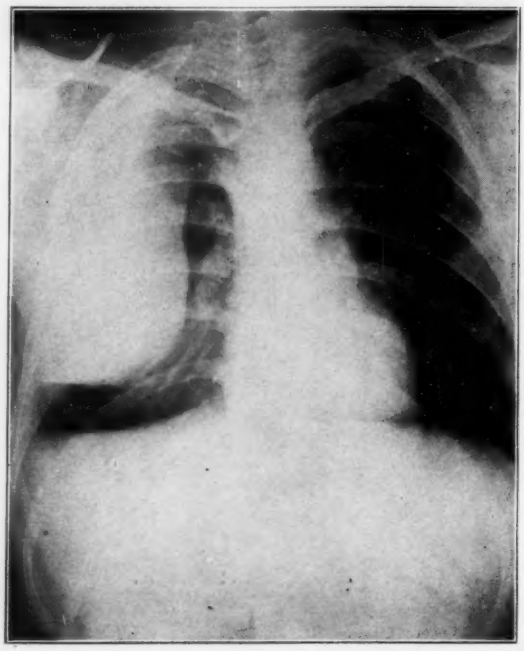

Fig. 3.—Encapsulated pleural effusion on right side of chest. Tubercle bacilli and Coccidioides immitis were recovered from the fluid.

He was discharged from military service in January 1946. The roentgenogram of the chest made at that time was interpreted as normal, but a routine preemployment roentgenogram, taken in May 1946, showed an apical cavity in the right lung. Reexamination of the separation film showed the same cavity. The patient was asymptomatic. The reaction to 1.0 mg. of old tuberculin was weakly positive. The coccidioidin skin test gave a positive reaction. Specimens of sputum were negative for tubercle bacilli and fungi. A roentgenogram of the chest taken in the lordotic position showed a cavity, measuring 3 by 3 cm., at the apex of the right lung. The cavity has remained unchanged for two years; the rest of the lung fields is normal, and the reaction to the coccidioidin skin test is still positive.

CASE 5.—Solitary round area of density. The patient had been assigned to an air field near Tucson, Ariz., from July 1942 to October 1945. In March 1945 he experienced pain in the chest, fever, dyspnea and loss of weight and a cough developed. A roentgenogram made on March 23, 1945 showed infiltration in the lower part of the left lung field and an increase in hilar density in the left lung. The coccidioidin skin test gave a positive reaction. Reactions to complement fixation and precipitin tests were positive. A follow-up roentgenogram taken on Jan. 28, 1948 showed a round area of density, 2.5 cm. in diameter, still present in the lower part of the left lung field. The density has not shown any change in almost three years, and the reaction to the coccidioidin skin test is still positive.

CASE 6.—Combined tuberculosis and coccidioidomycosis with persistent pleural effusion. The patient served in the Arizona desert in 1943. Acute primary

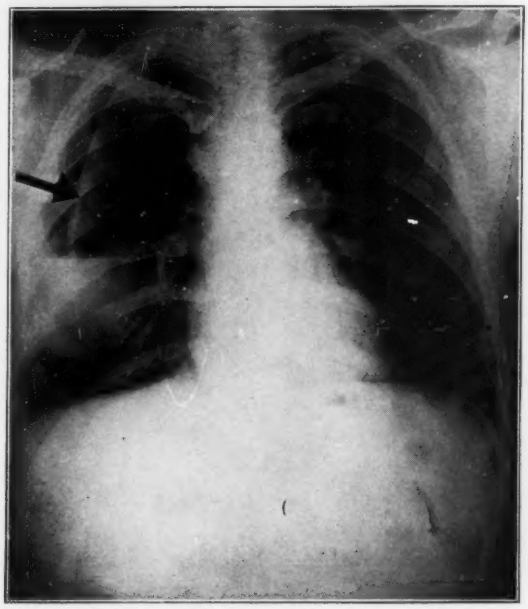

Fig. 4.—Hydropneumothorax on right side; round area of density at periphery of right lung; smaller round area of density at inner end of left third rib anteriorly.

coccidioidomycosis developed in September 1943. Roentgenograms of the chest showed bilateral pulmonary infiltrations. After partial resolution of these lesions, the patient was sent overseas. In August 1945 a febrile episode occurred. A roentgenogram showed hydropneumothorax on the right side. Cultures of the chest fluid revealed tubercle bacilli and C. immitis. Guinea pig inoculations also gave positive reactions for both diseases, and reactions to tuberculin and coccidioidin skin tests were positive.[5] The patient came under our observation in October 1947.

5. This was the status of the patient up to the point at which the case was reported by Rifkin and associates (Rifkin, H.; Feldman, D. J.; Hawes, L. E., and Gordon, L. E.: Coexisting Tuberculosis and Coccidioidomycosis, Arch. Int. Med. **79**:381 [April] 1947).

A roentgenogram made on October 29 (fig. 3) showed an encapsulated effusion of the right pleural cavity. After thoracentesis, a roentgenogram, on November 21 (fig. 4), showed hydropneumothorax on the right side, with a round area of density, 2 cm. in diameter, at the periphery of the right lung. There was a small, round area of density, also present on previous films, at the level of the left third rib anteriorly. The reaction to the coccidiodin skin test is still positive.

CASE 7.—Small nodule with calcification. The patient underwent desert training in the California-Arizona maneuver area from August 1943 to January 1944. He was hospitalized for a ten day period in November 1943 for a condition diagnosed as "pneumonia." In August 1944, while he was in England, infectious hepatitis

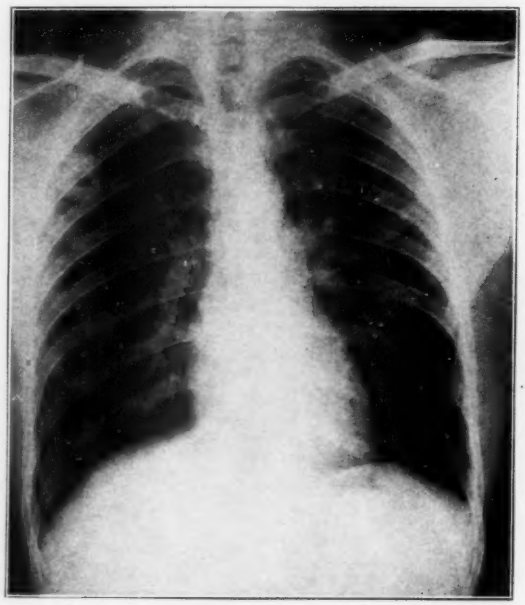

Fig. 5.—Thick-walled cavity behind right second rib anteriorly.

developed. A routine roentgenogram of the chest showed a round lesion in the upper part of the left lung field. Tuberculosis was suspected, but reactions to all tuberculin tests were negative. The reaction to coccidioidin was positive in a dilution of 1:1,000, and the complement fixation test gave a positive reaction. A roentgenogram of the chest on Jan. 29, 1947 showed a small, round area of density with central calcification at the left first interspace anteriorly.

CASE 8.—Bilateral cavities with spontaneous closure. The patient spent eight months in the Arizona desert in 1943. An acute infection of the upper respiratory tract developed while he was in the endemic area. In 1945, he had sudden hemoptysis while in the South Pacific. A roentgenogram of the chest showed thin-walled cavities in the upper field of both lungs. Reactions to skin tests with both coccidioidin and tuberculin were positive. Repeated examinations of the sputum failed

to reveal fungi or tubercle bacilli. Spontaneous closure of the cavities occurred in one year. A follow-up roentgenogram, taken on Sept. 26, 1947, showed bilateral residual fibrosis.

CASE 9.—Single thin-walled cavity and bilateral areas of fibrosis. The patient began desert training in West Texas in August 1944; fever, cough, pain in the chest and dyspnea developed two months later. A roentgenogram of the chest indicated a pneumonic infiltration in the right lung. Reactions to coccidioidin and tuberculin skin tests were positive, as were those to complement fixation and precipitin tests. A roentgenogram of the chest on Oct. 24, 1946 showed a residual, thin-walled cavity at the right second interspace anteriorly and bilateral infraclavicular fibrosis. A follow-up roentgenogram, made on Jan. 12, 1948, showed no change in the pulmonary cavity or in the rest of the lung fields. The reaction to the coccidioidin skin test is still positive; the serologic tests give weakly positive reactions

Fig. 6.—Disseminated coccidioidomycosis of the skin, showing pink, erythematous, granulomatous plaques on left lower portion of posterior wall of chest.

CASE 10.—Round area of density with central cavitation. The patient was stationed in the California-Arizona desert area from March to September 1943. A routine roentgenogram on his discharge from the Army, in December 1945, showed a cavity in the right lung. The coccidioidin skin test gave a positive reaction in a dilution of 1:1,000. Reactions to all tuberculin tests were negative, and specimens of sputum were negative for both fungi and tubercle bacilli. A roentgenogram of the chest on Sept. 11, 1947 (fig. 5) showed a cavity, measuring 3 by 3 cm., behind the right second rib anteriorly; comparison of this film with that of December 1945 revealed no change in the pulmonary lesion.

CASE 11.—Solitary oval nodule. The patient served in the Arizona desert from February 1944 to March 1945. A routine roentgenogram of the chest made at the time of discharge, in July 1945, showed a nodular lesion in the right lung. Reactions to skin tests with coccidioidin and tuberculin were positive. A roentgenogram of

the chest made on May 19, 1947 showed an oval area of density at the right second interspace anteriorly. Follow-up roentgenographic studies show no change in almost three years.

Case 12.—Bilateral nodular densities mistaken for metastatic carcinoma. While stationed in the Arizona desert for seven months in 1943, the patient experienced a febrile episode for ten days and was treated for "pleurodynia." A routine roentgenogram of the chest in July 1945 revealed bilateral nodular densities. The patient was asymptomatic and was separated from military service. A roentgenogram on April 12, 1946 again revealed the nodular densities in both lungs. A diagnosis of metastatic carcinoma of the lungs was made. A complete hospital study did not

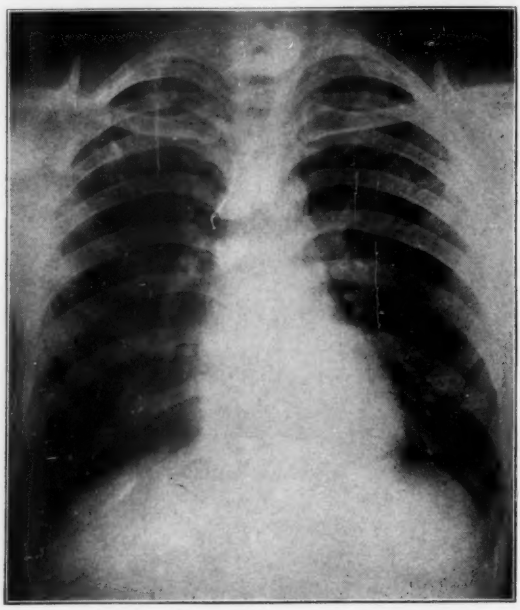

Fig. 7.—Mottled infiltration in upper parts of both lung fields.

confirm this diagnosis. A roentgenogram made on Sept. 3, 1947 showed an oval area of density in the left middle lung field and a small, round area of density in the right sixth interspace anteriorly. Reactions to both coccidioidin and tuberculin skin tests were positive. There has been no change in the pulmonary lesions in two and a half years.

Case 13.—Disseminated coccidioidomycosis. The patient was in the desert training area in California for three months in 1944. Ten months later, a cutaneous lesion developed on his back (fig. 6). A routine roentgenogram of the chest showed bilateral subclavicular mottled infiltrations. A diagnosis of lichen planus and pulmonary tuberculosis was made. The cutaneous lesions were treated for one year but failed to respond. Biopsy of the skin, performed on April 30, 1947 showed a coccidioidal granuloma with spherules in the tissue section. Reactions to coccid-

ioidin skin tests were negative (anergy). Complement fixation and precipitin tests gave positive reactions. At the time of writing, a roentgenogram of the chest (fig. 7) still shows a mottled infiltration in the upper parts of both lung fields.

COMMENT

Several pertinent observations were made in the cases described here as well as in the other 7 cases which comprised the study:

1. The residual lesions were of all types, i.e., nodular densities, cavities, mottled infiltrations, fibrosis, pleural effusion and calcification.

2. These residual pulmonary lesions characteristically showed little or no change over a period of observation of from two to five years.

3. All patients gave a history of residence in the endemic area, varying from three months to two years.

4. Skin sensitivity to coccidioidin was observed to diminish with the lapse of time.[6] However, Smith and associates[7] asserted that sensitivity to coccidioidin is durable and that, although it may wane, its loss is usually slow. Thus, while a dilution of 1:1,000 commonly yields strong reactions in early cases, it was found preferable to employ 1:100 and 1:10 dilutions in our (residual) cases. All the patients in this series reacted to coccidioidin in 1:100 dilution. The reactions were usually of a mild type (1 or 2 plus), in contrast to the stronger type of reaction (3 or 4 plus) which one of us (H. E. B.)[4] had seen in a large group of relatively early cases.

5. A negative reaction to the coccidioidin skin test was misleading in the presence of a disseminating lesion. In such an instance (case 13) the failure to react to coccidioidin was presumed to be related to anergy. However, serologic examination is usually diagnostic and can often be confirmed by recovery of the spherules in a tissue biopsy, from sputum or from draining sinuses.[8]

6. In cases of cavity formation, no evidence of bronchogenic spread or of seeding to other parts of the lung fields, such as occurs commonly in tuberculosis, was observed.

7. The resemblance of the residual pulmonary lesions to those in tuberculosis was striking. In several of the cases, a diagnosis of tuberculosis had been made after the patient's return to civilian life, usually after a routine chest survey or preemployment roentgenoscopic examination. In a number of cases, a positive reaction to both the tuberculin

6. Cheney, G., and Denenholz, E. J.: Observations on Coccidioidin Skin Test, Mil. Surgeon **96**:148 (Feb.) 1945.

7. Smith, C. E.; Whiting, E. G.; Baker, E. E.; Rosenberger, H. G.; Beard, R. R., and Saito, M. T.: The Use of Coccidioidin, Am. Rev. Tuberc. **57**:330 (April) 1948.

8. Smith, C. E.: Coccidioidomycosis, M. Clin. North America **27**:790 (May) 1943.

and the coccidioidin skin test made diagnosis difficult. In such cases a presumptive diagnosis of coccidioidomycosis was made on the basis of the following evidence: (*a*) history of exposure in an endemic area; (*b*) roentgenographic evidence of a pulmonary lesion, usually a solitary cavity or nodular density, which showed no change after months of observation; (*c*) indication of an identical lesion in the roentgenogram of the chest taken on separation from military service; (*d*) a positive reaction to the coccidioidin skin test, and (*e*) absence of tubercle bacilli.

8. Almost all the patients observed were asymptomatic. The notable exceptions included a patient with a cavity who had recurrent hemoptyses, a patient with pleural effusion (case 6) and the single patient with disseminated disease (case 13).

SUMMARY

Twenty veterans of World War II with residual lesions of pulmonary coccidioidomycosis have been observed. Thirteen cases are described.

The residual lesions persisted from two to five years after the initial infection.

The importance of differential diagnosis from other pulmonary diseases, particularly tuberculosis, is emphasized.

CONCLUSIONS

Coccidioidomycosis should no longer be considered a rare disease confined to a small endemic area (the San Joaquin Valley in California). At present the endemic areas in the United States include West Texas, southern New Mexico, southern and central Arizona, southwest Utah, and possibly southern Nevada, and a number of areas in southern California, in addition to the San Joaquin Valley.[9] The incidence of infection in military personnel who spent part of their military service in the endemic areas was high (25 per cent). Increased travel facilities and the popularity of motor car travel (merely driving through an endemic area can result in infection) are additional factors of importance in the incidence of this disease.[9] Any person who presents a pulmonary infiltration in which the diagnosis cannot be readily established should be questioned as to exposure in an endemic area. If such a history of exposure is obtained from one who reacts to coccidioidin, a presumptive diagnosis of pulmonary coccidioidomycosis should be made.

9. Smith, C. E.: Recent Progress in Pulmonary Mycotic Infections, California Med. **67**:179 (Sept.) 1947.

ANTIBIOTIC THERAPY FOR CUTANEOUS ANTHRAX

Report of Five Cases

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IT IS our purpose to outline the favorable results of treating cutaneous anthrax with penicillin and sulfadiazine in 4 cases and with streptomycin in 1. We think that this is the first report of the use of streptomycin in cases of human anthrax. Streptomycin used in vitro is successful.[1]

It is claimed that the incidence of anthrax is rising in the United States. A survey of the United States Public Health Service discloses the data in the accompanying table.

Incidence of Anthrax

	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
United States	65	54	57	79	105	97	72	49	44	36	64
Arkansas	0	4	0	2	0	2	1	1	0	0	7

The animal colonies in Arkansas have been heavily infected during late years in the lowlands, particularly in Arkansas and Cross Counties. New endemic areas have appeared about Nashville, which is unusual. In 1942, 3,000 cattle, horses and hogs were reported to have anthrax, and perhaps there were many more not reported. Fifteen thousand animals were given prophylactic inoculation against anthrax during that year. As the incidence of anthrax diminishes, farmers are not so attentive to immunization of their animals. At present about one eighth of the animals in the areas in Arkansas in which anthrax is prevalent are immunized.

For many years there has been a greater incidence of human anthrax in the United States in areas, i. e., the Atlantic seaboard, in which infected hides from foreign countries, Arabia and Egypt, were processed. The recent war naturally diminished the high incidence of anthrax

From the Departments of Medicine and Pediatrics, University of Arkansas School of Medicine.

1. Miller, E. S.; Scott, E. B.; Noe, H. A.; Madin, S. H., and Henley, T. F.: Chemotherapy of Experimental Anthrax Infections, J. Immunol. **53**: 371-379 (Aug.) 1946.

in the states of New York and Pennsylvania. But a false sense of security led to more frequent occurrence of anthrax in animals in the range states, and promiscuous distribution of cattle products by the black market possibly raised the incidence.

REPORT OF CASES

Cases 1, 2 and 3.—C. J., D. J. and C. H. were white men aged 29, 31 and 33. Two (aged 31 and 33) were brothers, and the youngest was a relative by marriage. On Sept. 10, 1947, the three men saw a cow fall in a neighbor's pasture and on informing the neighbor were told that they could have the animal. They skinned the animal while it was still warm, and within twenty-four to forty-eight hours the malignant pustules and edema typical of anthrax lesions had begun to develop. The other initial symptoms were severe headaches, malaise and high temperature. The lesions were multiple in all cases on the hands and forearms and were at the site of previous abrasions from briar scratches or lacerations incurred in skinning the animal. There was regional adenopathy. The 31 year old man had symptoms first, and he was taken to a local physician, who gave him several injections of penicillin which did not alter the appearance of the lesions. Lesions developed on the other 2 men on September 13, and all 3 were sent to the isolation ward at the University of Arkansas Hospital. The diagnosis was made from smear, culture and the typical appearance of the lesions. Cultures were sent to the bacteriology laboratory for study of the sensitivity of the organisms to penicillin and streptomycin. They were sensitive to both. In the 3 cases penicillin, 50,000 units every three hours intramuscularly, and sulfadiazine, 4.0 Gm. initially and 1.0 Gm. every four hours for five days, were administered, and the lesions were treated locally with gentian violet and dry dressings to prevent further spread of infection. In all cases the symptoms disappeared and the malignant edema was absent after forty-eight hours of treatment. The patients were discharged on the eighth day from the hospital; the lesions were dry and much smaller than they were on admission, and the smears were sterile.

Case 4.—E. H., a 27 year old white woman, was the wife of patient C. H. (case 3). She had not come in contact with the animal that the three men had skinned, nor had she come in contact with the instruments used. She had dressed the anthrax lesions of her husband on Sept. 14, 1947. On September 16 a typical lesion of anthrax developed at the site of a healing paronychia of her left middle finger. Smears of this lesion yielded the organisms of anthrax. The lesion was treated locally with gentian violet and bandaged, and the patient was given penicillin in oil and white wax intramuscularly, 300,000 units daily, and sulfadiazine, 4 Gm. for the initial dose, and 1 Gm. every four hours, as an outpatient and confined to her quarters. The treatment was continued for five days, at which time the swelling and tenderness had disappeared and the lesion was healing rapidly. Epitrochlear and axillary adenopathy had disappeared at this time.

Case 5.—A 15 year old boy was a butcher's helper. He helped to skin an animal that had died of what later was proved to be anthrax by the state veterinarian. Thirty cattle had died from anthrax in the area during the months of September and October. On Oct. 12, 1947, the patient noticed a small vesicular lesion on the volar surface of his right forearm. By October 13 this lesion had become extremely dark and there was considerable swelling for several inches

around the dark center. There was regional adenopathy. That night the patient began to have fever, and he felt exceedingly ill. He was admitted to the hospital on October 16, after a diagnosis of anthrax had been made by the local physician. Smear and cultures did not reveal the presence of anthrax, and agglutination tests for tularemia gave negative results. The principal symptoms on the patient's admission to the hospital appeared to be typical of anthrax, and there were malignant pustules, malignant edema and lymphadenopathy of the right axillary region. The temperature was 99.6 F., the pulse rate 120 and the respirations 20. The patient had a preexisting and apparently unrelated chronic glomerulonephritis. In view of the renal disease, which might have been complicated by sulfonamide therapy, and on the basis of successful eradication of anthrax in animals with streptomycin, it was decided to treat the patient with the latter drug. Within twenty-four hours after an initial dose of 500 mg. intramuscularly and 250 mg. every three hours for five days the patient was definitely improved. The edema had almost disappeared, and slight fever continued only twelve hours longer. The axillary lymphadenopathy had disappeared on October 22. The patient was discharged on the tenth day; the dry desquamating area, 3 cm. across, had a small eschar thereon.

The patients in cases 1, 2, 3 and 4 were given daily 300,000 units of penicillin and sulfadiazine for five days. Improvement started within twenty-four hours and continued thereafter. This amount of penicillin was large compared with that given by Murphy and others,[2] which was roughly 325,000 to 475,000 units during seventy-five hours only. Cultures of material from their patients became sterile as early as the second day and usually by the fifth day of therapy. Smears usually are sterile before this. Ellingson and others,[3] using 1,000,000 to 4,000,000 units of penicillin in 25 cases of cutaneous anthrax, in 3 of which bacteremia was also present, demonstrated sterile lesions in 21 cases. Unfortunately, our only bacteriologic check was the demonstration of sterile smears on the eighth day in the first 3 cases. However, the improvement in all 4 was quick in onset and progressively more notable daily. We did detect some evidence of the "tissue damaging factor" of Bacillus anthracis,[3] but it was only slight. This damage, probably due to the toxin, continues to operate for a short time after the organisms have been killed by the penicillin.

We realized that the diagnosis of anthrax was not clearly proved in case 5 because smears and cultures did not reveal the disease. Since the history, the physical findings, the number of deaths from anthrax in animals and the laboratory tests ruled out other causes, we have no doubt that the lesions were due to this disease.

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2. Murphy, F. D.; La Boccetta, A. C., and Lockwood, J. S.: Treatment of Human Anthrax with Penicillin: Report of Three Cases, J. A. M. A. **126:** 948-950 (Dec. 9) 1944.

3. Ellingson, H. V.; Kadull, J. P.; Bookwalter, H. L., and Howe, C.: Cutaneous Anthrax: Report of Twenty-Five Cases, J. A. M. A. **131:** 1105-1108 (Aug. 3) 1946.

Miller and his collaborators [1] showed that 93 per cent of mice infected with anthrax survived when adequately treated for seven days with penicillin and 5 per cent survived when treated for seven days with sulfadiazine. We cannot find a previous reference to the use of streptomycin for human anthrax, and we are of the opinion that this is the first such report. Culturally, this antibiotic prevents the growth of the anthrax bacillus.

Our dosage of streptomycin was in keeping with the normal amount recommended for its proper usage. It will be noted that the patient's toxicity and the malignant appearance of the lesions improved greatly within the first twenty-four hours, the fever disappeared after thirty-six hours and axillary lymphadenopathy was barely palpable, the areas being no longer tender, by the sixth day of treatment with streptomycin. The renal lesion slowly improved and was not aggravated. It is possible that the dosage of the drug and the duration of its administration could have been decreased.

COMMENT

In our cases the cutaneous anthrax may have been naturally mild. How much time would have been required for a spontaneous uncomplicated cure is problematic. While we combined sulfadiazine with penicillin and recognized the effectiveness of either in this disease,[2] it is our feeling that the latter is the more efficient of the two and that we could have dispensed with the use of sulfadiazine. Some feel that the combination of a sulfonamide compound with penicillin is the most desirable therapy. Gold [4] stated that sulfathiazole is the most effective of the sulfonamide drugs. Exactly what penicillin alone would do for the majority of septicemic and pulmonic forms is difficult to predict, but the observations of Murphy and others,[2] who successfully treated 3 patients with the cutaneous form as well as septicemia, are most encouraging. The patient in our case 5 may also have had the septicemic form.

A choice between penicillin and streptomycin for therapy in human beings would at present probably favor penicillin for it has more effectively suppressed cultural growth of anthrax, it is more widely distributed and it costs less since only 100,000 to 200,000 units daily for five to seven days is required. As streptomycin is studied more in connection with anthrax, it may prove to be the better drug. A sensitivity test with the two antibiotics is very desirable when there is doubt, as, for instance, when a patient has cutaneous anthrax and septicemia. The anthrax cultures in cases 3 and 4 were sensitive as

4. Gold, H.: Anthrax: Review of Sixty Cases, with Report on Therapeutic Use of Sulfonamide Compounds, Arch. Int. Med. **70**: 785 (Nov.) 1942.

follows: One cubic centimeter of positive nutrient broth culture (Difco medium) showed no growth with 3 units and some growth with 1½ unit, of penicillin and no growth with 1/5,120 mg. and some growth with 1/10,240 mg. of streptomycin.[5] This result helped us choose streptomycin for therapy in case 5.

SUMMARY

Five cases of cutaneous anthrax are briefly described. Four patients were given daily 300,000 units of penicillin and 6 Gm. of sulfadiazine for five days; the fifth received daily 2 Gm. of streptomycin for five days. No fatalities occurred; improvement was noted within twenty-four hours, and thereafter progress was rapid. Review of the literature shows that doses of only 100,000 to 200,000 units of penicillin daily for three days have sterilized the lesions of cutaneous anthrax. Longer treatment, however, is safer. This is the first case report of the successful use of streptomycin for human cutaneous anthrax and the first report of transmission of anthrax from one human being to another by direct contact.

5. Dr. James T. Culbertson, professor of bacteriology, University of Arkansas School of Medicine, specially carried out these tests.

RESPIRATION AND CIRCULATION IN PULMONARY ANOXEMIA

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THE ANOXEMIA of pulmonary diseases differs from that found in persons at high altitude, mainly because arterial carbon dioxide tension and hydrogen ion concentration increase in the former and decrease in the latter. To estimate the importance of carbon dioxide and/or hydrogen ion in circulatory and respiratory adjustment, results in patients with Ayerza's disease were compared with those secured in patients with anoxic conditions without carbon dioxide retention, i.e., in patients at high altitude and in those with congenital heart disease.

At present some of the mechanisms of respiratory and circulatory regulation are not completely clear. It was thought that the comparative study of these functions in various types of anoxia could throw light on the subject. For that reason it was decided to investigate the circulatory and respiratory function in three different types of anoxia: (*a*) anoxic anoxia due to impairment of the pulmonary function, with low arterial oxygen tension and carbon dioxide retention; (*b*) anoxic anoxia due to shunt of blood from the right side of the heart to the left through unaerated channels, with low arterial oxygen tension without carbon dioxide increase; (*c*) anemic anoxia in which arterial carbon dioxide and oxygen tensions are normal, but tissular anoxia is present.

The present paper deals with pulmonary anoxia.

MATERIAL

Determinations were made on 18 patients with different degrees of pulmonary fibrosis and emphysema. Sixteen were male and two female, 2 of the former being smokers. All patients complained of cough for a long time and had had acute bronchitis repeatedly. Eight had also had asthmatic attacks.

All patients complained of dyspnea. In 16 cases there was a definite cyanosis, and in 8 there was a fully developed picture of Ayerza's syndrome.

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The diagnosis was made on the basis of clinical and roentgenologic examination. In table 1 are listed the main symptoms and signs in every case, and it can be seen there that 8 of the patients studied had heart failure. Several elements were considered for the diagnosis of cardiac failure: enlargement of the heart, gallop rhythm, tricuspid murmur, engorgement of the liver, high venous pressure and prolonged circulation time. Dyspnea, common among these patients, was considered as a sign of heart failure only if it was present at rest and in the absence of bronchial spasm. Since edema is frequently found among these patients in the absence of heart failure, this sign was considered only when it was extensive and was accompanied with hepatic engorgement and high venous pressure.

METHODS

All the determinations were made with the subjects under basal conditions. They were placed in bed in a comfortable, quiet room, and they rested for at least thirty minutes. In some cases the sitting position was used.

Arterial Blood.—The femoral artery was punctured with a 1 mm. bore needle and blood received in a 30 cc. syringe coated with paraffin oil. It was immediately transferred under paraffin to a 50 cc. tube which contained heparin solution (1 drop for each 10 cc. of blood), mixed gently with a glass rod and finally transferred to a blood-sampling tube under mercury. The tube was sealed with mercury and kept in the refrigerator until analysis was made.

Tonometers.—For the determination of the acid-base equilibrium and the oxygen capacity, only one tonometer is needed. All necessary determinations were made from the blood in the tonometer and from the arterial blood as drawn, as will be shown later. Enough oxygen and carbon dioxide were added to the tonometer to obtain pressures of 190 and 40 mm. of mercury and oxygen tensions of 20, 30, 40, 60 and 190 mm., respectively. About 6 cc. of blood was introduced in each tonometer and equilibrated with the gas in a water bath at 37 C. during fifteen minutes. After the blood was transferred into sampling tubes under mercury, the pressure of the gases in the tonometer was measured with a small mercury manometer. Duplicate analyses of the carbon dioxide and oxygen were carried out in a Haldane apparatus. The oxygen and carbon dioxide pressures of the tonometer at the bath temperature were calculated with the formula:

$$pCO_2 \text{ or } pO_2 = C\ (B\text{–}w + pp) \quad \frac{273 + 37}{273 + t} \times \frac{V\text{–}6 + 5}{V\text{-}6}$$

in which pCO_2 and pO_2 indicate partial pressure of carbon dioxide and oxygen in millimeters of mercury, C content of carbon dioxide or oxygen in volumes per cent, B barometric pressure in millimeters of mercury, w vapor pressure at room temperature, pp pressure of tonometer (to be subtracted if negative), t room temperature in degrees centigrade, V volume of tonometer in cubic centimeters, 6 volume of blood present in the tonometer during equilibration and 5 volume of blood taken from the tonometer for analysis.

Equilibrated and arterial blood as drawn was analyzed for oxygen and carbon dioxide contents in a Van Slyke-Neill apparatus. Duplicate analyses were carried out using 1 or 0.5 cc. of blood. Determinations agreed within 0.2 volume per cent of oxygen and 0.5 volume per cent of carbon dioxide.

TABLE 1.—*Clinical Data on the Eighteen Patients Studied**

Case	Age	Sex	Lungs				Heart								
			Emphysema	Fibrosis	Asthma	Sclerosis of Pulmonary Branches	Enlargement of Right Ventricle	Dilatation of Pulmonary Trunk	Right Axis Deviation	Right Heart Failure	Blood Pressure	Dyspnea	Cyanosis	Edema	Red Blood Cell Count
1	60	M	+*	+++	—	+++	++	+	—	—	160/80	+++	++	++	6,400,000
2	46	M	+	+	—	+	+	+	+	—	130/90	++	+	—	5,800,000
3	53	M	+	+	—	+	+	++	—	+	180/120	+++	++	+	6,300,000
4	40	M	++	++	++	++	+	++	+	+	170/105	++	+++	+	7,300,000
5	49	M	+++	++	—	++	—	+++	—	—	150/105	++	+	—	5,600,000
6	55	M	++	+++	++	++	++	+	—	—	140/85	++	+	—	4,500,000
7	35	M	++	+	++++	++	+	++	+	+	170/110	+++	++	++	6,700,000
8	52	M	+	++	+++	++	+	++	—	—	135/110	+++	+++	—	6,900,000
9	58	M	++	++	++	++	+	+	+	—	125/80	+++	+++	—	5,600,000
10	64	M	++	++	—	++	++	++	+	+++	170/110	++	++++	+++	7,600,000
11	..	M	++	+++	—	+++	++	+	+	++	125/70	+++	+++	+	6,400,000
12	..	M	+++	+++	—	+++	+++	++	+	+++	135/85	+++	++++	++	6,410,000
13	51	M	+	+	++	+	++	+	+	+++	155/110	+++	+++	+++	7,500,000
14	62	M	+	+++	—	++	+++	++	—	+++	180/120	+++	+++	++++	6,900,000
15	54	M	++	+++	—	+++	+++	++	+	++++	120/80	++++	++++	++++	7,400,000
16	..	M	++	++	++	++	+	++	—	—	220/115	++	+	—	4,700,000
17	56	F	+	++	++	++	+	++	—	—	100/70	++	—	—	4,000,000
18	58	F	+	+++	—	++	+	++	—	—	160/100	++	—	—	4,300,000

* One plus sign indicates slight; 2 plus, mild; 3 plus, pronounced and 4 plus, severe.

Calculation of Carbon Dioxide Tension and p_H of the Arterial Blood.—With carbon dioxide and oxygen tension and content of the blood equilibrated into the tonometer as the known variables, the carbon dioxide tension of the arterial blood as drawn was calculated from its carbon dioxide content and oxygen saturation, Henderson's nomogram being used. The carbon dioxide content of plasma was calculated from the values of the carbon dioxide content of the blood at 40 mm. of mercury and complete saturation, and the oxygen capacity of the blood by means of the cartesian chart constructed by Henderson and others.[1] The p_H of plasma was calculated by the Henderson-Hasselbalch equation. Free carbon dioxide of serum was obtained from the carbon dioxide tension, with the use of the solubility coefficient of Van Slyke and his associates[2] and bicarbonates by subtracting free carbon dioxide from the total carbon dioxide content of the plasma. The value 6.11 for pK found by Dill, Daly and Forbes[3] in normal serum at 37 C. was used.

Oxygen Tension of the Arterial Blood.—The oxygen tension of arterial blood was calculated by interpolating the oxygen saturation of the arterial blood in the oxyhemoglobin dissociation curve (corrected for the arterial p_H). A standard curve was used when no oxygen dissociation curve for the subject was available.

Oxygen Dissociation Curve.—Points on the oxygen dissociation curve were obtained by equilibrating the blood into the tonometers with oxygen tensions of 20, 30, 40 and 60 mm. of mercury and carbon dioxide tension of 40 mm. Other steps were carried out as described previously. The oxygen dissociation curve was plotted to show $\frac{\text{Hb } O_2}{\text{Hb}} \times 100$ as a function of oxygen tension at p_H 7.40. To correct for derivations from p_H 7.40 in the various tonometers, log $\frac{100 \text{ Hb}}{\text{Hb } O_2}$ was plotted as a function of log pO_2. This logarithmic dissociation curve has the advantage over the usual curve in that the effect of a given change in p_H on log pO_2 is the same for practically all values of log $\frac{100 \text{ Hb}}{\text{Hb } O_2}$. According to Dill (in a personal communication) a change of a unit in p_H will produce a corresponding change of 0.479 in log pO_2.

Water in Plasma and Red Cells.—The determinations were carried out on arterial blood equilibrated with oxygen and carbon dioxide in a tonometer at pressures of 190 and 40 mm. of mercury, respectively. After equilibration, blood was transferred under oil to a 10 cc. centrifuge tube described by Peters and Van Slyke.[4] After centrifugation at 3,000 revolutions per minute during forty-five

1. Henderson, L. J.; Bock, A. B.; Dill, D. B., and Edwards, H. T.: Blood as a Physicochemical System: IX. The Carbon Dioxide Dissociation Curves of Oxygenated Human Blood, J. Biol. Chem. **87**:181, 1930.

2. Van Slyke, D. D.; Sendroy, J.; Hastings, A. B., and Neill, J. M.: Studies of Gas and Electrolyte Equilibria in Blood: X. The Solubility of Carbon Dioxide at 38° in Water, Salt Solution, Serum and Blood Cells, J. Biol. Chem. **78**:765, 1928.

3. Dill, D. B.; Daly, C., and Forbes, W. H.: The pK of Serum and Red Cells, J. Biol. Chem. **117**:569, 1937.

4. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, London, Baillière, Tindall & Cox, 1932, vol. 2, p. 56.

minutes, the plasma was separated and a measured amount, about 1 cc., placed in a small weighing bottle. The upper portion of the packed cells was discarded and a sample of the bottom weighed in a weighing bottle. Cells and plasma were dried at 110 C. to constant weight. Cell's water $(H_2O)_c$, in cubic centimeters of water per liter of cells, was calculated with the formula: specific gravity equals 1.300—0.3 (water per gram of cells).[5]

Chlorides.—Chlorides were determined in the anaerobically separated plasma and red cells by the method of Van Slyke and Sendroy modified by Eisenman.[6]

Bicarbonates in Red Cells and Plasma.—Blood was equilibrated into a tonometer with carbon dioxide at a pressure of 40 mm. of mercury and oxygen at a pressure of 190 mm., being thereafter transferred to (*a*) a blood-sampling tube under mercury, (*b*) a hematocrit tube and (*c*) the anaerobic centrifuge tube described by Peters and Van Slyke. Sample *c* was centrifuged at 3,000 revolutions per minute during ten minutes to minimize the carbon dioxide loss. Analysis of carbon dioxide in the separated plasma and in the total blood was carried out in the Van Slyke-Neill apparatus and carbon dioxide content of the red cells calculated from these values; the hematocrit readings were determined with the following formula:

$$(TCO_2)_c = \frac{(TCO_2)_b - (TCO_2)_s \cdot Vs}{Vc}$$

in which $(TCO_2)_c$, $(TCO_2)_b$ and $(TCO_2)_s$ indicate total carbon dioxide of the red cells (c), blood (b) and plasma (s) in volumes per cent and Vs and Vc volumes of serum (s) and cells (c).

p_H of Red Cells.—$(p_H)_c$ was calculated with the use of the Henderson-Hasselbalch equation. Free carbon dioxide of the cells was obtained from carbon dioxide pressure with the use of the solubility coefficient of Van Slyke, Sendroy, Hastings and Neill [2] as recalculated by Dill, Daly and Forbes [3] at 37 C. The value used for $pk')_c$ (oxygenated blood) was 6.04 as found by the latter authors.

r, the distribution of electrolytes between plasma and cells, was calculated as follows:

$$r\ Cl = \frac{(Cl)_c}{(Cl)_s} \times \frac{(H_2O)_s}{(H_2O)_c} \qquad r\ BHCO_3 = \frac{(BH\ CO_3)_c}{(BH\ CO_3)_s} \times \frac{(H_2O)_s}{(H_2O)_c}$$

$$rH = \frac{(H)_s}{(H)_c} \times \frac{(H_2O)_s}{(H_2O)_c}$$

Respiratory Volume.—Respiratory volume was determined in subjects already familiarized with the procedure while lying in bed in a comfortable, quiet room. Patients inspired room air or various gas mixtures through a mouth piece from a 600 liter gasometer; gas volume and cardiac and respiratory rates were taken every minute for twenty minutes. Correctness of the gas mixtures was controlled by analysis in a Haldane apparatus before and at the end of the experiment.

Lung Volume and Its Subdivisions.—A Sanborn-Benedict metabolism tester was used, with the soda lime container outside the spirometer and with a bell capacity of 8 liters. All determinations were made with the subject in a sitting position. Vital capacity and reserve and complemental air were determined in

5. Horvath, S. M.; Consolazio, W. W., and Dill, D. B.: Syllabus of Methods of the Fatigue Laboratory, Harvard University.

6. Eisenman, A. J.: A Note on the Van Slyke Method for the Determination of Chlorides in Blood and Tissue, J. Biol. Chem. **82**:411, 1929.

the usual way. The difference between the normal expiratory level and the level of maximal inspiration was computed as complemental air. Residual air was measured in duplicate with Christie's method [7] as modified by Robinson,[8] the subjects being connected to the spirometer while they were in the position of maximal expiration.

Gas analysis of the final mixture was carried out in duplicate in a Haldane apparatus, dilution or storage technics, with frequent testing for carbon dioxide, being used.

All volumes are expressed in liters of air saturated with water vapor at 37 C. and the prevailing pressure (B. T. P. S.).

Alveolar Air.—A curved glass tube with a 20 mm. bore and about 100 cc. capacity was employed; it was connected through a three way stopcock to the mouth piece and with a Mueller water valve in the opposite end. The subject, with the mouth piece and the nose clip adjusted, was asked to blow toward the end of a normal expiration; the cock was turned back as expiration was completed and a sample withdrawn from the tube.

In cases in which there is respiratory disease it is often difficult for the patient to expire as fast as he is required. In such cases the amount of gas expelled was measured, and if it proved to be greater than 600 cc. in four seconds the sample was secured at this time.

Serial Determinations of Alveolar Air.—Subjects were connected through a mouth piece and a three way cock to a long rubber tube attached to a recording spirometer. Four gas-sampling tubes, previously evacuated, were attached to sampling outlets on that part of the cock carrying the rubber tube. After the apparatus was flushed with alveolar air, the subject was asked to blow as fast and as far as he could. Gas samples were taken within the first six seconds after about 500, 900 and 1,300 cc. of expired air had been received. In some patients the expiration was so slow that only two samples could be obtained in that period, the first after 500 cc. was received and the last at the end of the six second period (the volume of air expired at the moment the last sample was taken was variable).

Cardiac Output.—All determinations were carried out with the patients sitting in a comfortable armchair at an angle of 105 degrees and with flexed knees. In every case the patient had been previously trained to carry out the procedures.

The arteriovenous oxygen difference was determined with Grollman's [9] acetylene method, four samples being taken during the rebreathing period. The gas analyses were performed in a Haldane apparatus equipped with a 12 cc. burette and with a device for acetylene absorption.

The oxygen consumption was determined by the open circuit method using a 100 liter gasometer, the air being collected during ten minute periods. These data were also used to calculate the basal metabolic rate according to the normal standards of Aub and Du Bois and then to calculate the ratio of pulmonary ventilation to oxygen consumption (ventilation equivalent for oxygen), which we used to express as cubic centimeters of pulmonary ventilation for each cubic centimeter of oxygen absorbed under similar conditions.

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7. Christie, R. V.: The Lung Volume and Its Subdivisions: I. Methods of Measurement, J. Clin. Investigation **11**:1099, 1932.

8. Robinson, S.: Experimental Studies of Physical Fitness in Relation to Age, Arbeitsphysiol. **10**:251, 1938.

9. Grollman, A.: The Determination of the Cardiac Output of Man by the Use of Acetylene, Am. J. Physiol. **88**:432, 1929.

Blood Volume.—Determinations of blood volume were carried out by the injection of Evans blue (T 1824) according to Gibson and Evans' method [10]; four samples were taken fifteen, thirty, forty-five and sixty minutes after the injection of the dye. Readings were made on separated plasma with the Evelyn photoelectric colorimeter.

Cells and total blood volumes were calculated from hematocrit values, the latter being obtained on heparinized blood after forty-five minutes of centrifugation.

Venous Pressure.—This was measured in the arm, with the subject in the recumbent position, by the technic described by Lyons, Kennedy and Burwell.[11]

Circulation Time.—Intravenous injection of 5 cc. of 20 per cent "decholin" solution was used for the arm to tongue circulation time; 0.2 cc. of ether in 1 cc. of sodium chloride solution was used for the arm to lung circulation time.

Statistical Treatment.—In the statistical evaluation of the results, the following equations were used: for the standard deviation, $\sigma = \sqrt{\frac{\Sigma\ d^2}{(n\text{-}1)}}$; for the standard error, $\epsilon = \sqrt{\frac{\Sigma\ d^2}{n(n\text{-}1)}}$. In groups with less than 10 cases the equation employed for the calculation of ϵ was $\sqrt{\frac{\Sigma\ d^2}{(n\text{-}1)\ (n\text{-}1)}}$.

In comparison of the different groups, the standard deviation of the difference between the averages was calculated according to the equation $\sqrt{\epsilon_I^2 + \epsilon_{II}^2}$. The differences were considered statistically significant when they were equal to or greater than three times their standard error.

RESULTS

Alveolar Air.—As is shown in table 2, the carbon dioxide tension of the alveolar air ranged from 38.6 to 63.9 mm. of mercury, with an average of 51.8 mm. For a group of normal subjects of the same age (40 to 60 years), Robinson [8] found a mean value of 41 mm., the upper value being slightly over 45 mm. In 12 of our 16 patients the alveolar carbon dioxide tension was found to be over 45 mm. of mercury; in the remaining 4 it was within the normal range.

On the other hand, the oxygen pressure of the alveolar air ranged between 60.6 and 98.5 mm., with an average of 78 mm., being in 10 cases lower than 85 mm., the lowest value found by Robinson in the previously mentioned group of normal subjects.

These results are in accordance with the findings of Meakins and Davies (1925)[12] and of Christie [13] in cases of emphysema and with

10. Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, J. Clin. Investigation **16**:301, 1937.

11. Lyons, R. H.; Kennedy, J. A., and Burwell, C. S.: The Measurement of Venous Pressure by the Direct Method, Am. Heart J. **16**:675, 1938.

12. Meakins, J. C., and Davies, H. W.: Respiratory Function in Disease, Edinburgh, Oliver & Boyd, 1925.

13. Christie, R. V.: The Elastic Properties of the Emphysematous Lung and Their Clinical Significance, J. Clin. Investigation **13**:295, 1934.

TABLE 2.—*Lung Volume and Pulmonary Ventilation* *

Case	Respiratory Rate, per Minute	Pulmonary Ventilation, L./Sq. M.	Tidal Air, Liters	Vital Capacity, Liters	Reserve Air, Liters	Complemental Air, Liters	Residual Air, Liters	Functional Residual Air, Liters	Total Capacity, Liters	Residual Air, Total Capacity, per Cent	Functional Residual Air, Total Capacity, per Cent	Basal Metabolic Rate, per Cent	Ventilation Equivalent, Cc. O_2	CO_2 in Expired Air, per Cent	Alveolar Air	
															CO_2, Mm. Hg	O_2, Mm. Hg
2	18	4.08	0.40	2.54	0.72	1.82	2.48	3.20	5.02	49.4	63.8	— 0.5	26.3	3.15	62.1	63.0
															63.8	61.1
3	12	4.13	0.70	3.81	1.04	2.77	2.45	3.48	6.26	39.1	55.6	— 2.5	26.9	3.06	38.6	98.5
4	16	4.02	0.41	3.68	1.23	2.45	2.05	3.28	5.73	35.8	57.2	+ 7.2	27.2	3.19	46.8	92.5
															47.5	85.7
5	9	3.33	0.67	....	....	....	....	....	....	....	....	....	....	....	45.6	96.2
6	17	5.43	0.53	2.27	1.10	1.17	2.52	3.62	4.79	52.6	75.6	+ 1.0	34.8	2.40	41.4	95.5
7	16	4.22	....	2.80	1.18	1.63	....	....	....	....	....	....	....	....	63.0	57.0
8	11	4.08	0.50	2.41	1.06	1.35	3.04	4.10	5.45	55.8	75.2	+20.0	24.1	3.33	63.9	67.8
															61.4	72.6
9	18	4.69	0.42	....	....	....	....	....	....	....	....	+ 3.2	28.8	2.78	....	....
10	19	....	....	2.26	1.00	1.26	1.65	2.65	3.91	42.2	67.8	+ 7.0	37.6	2.10	38.7	95.4
	11	5.68	0.60	2.32	0.94	1.38									42.9	87.0
															38.2	97.0
11	22	4.69	0.41	2.80	0.80	2.00	1.00	1.80	3.80	26.3	47.4	+19.0	24.3	2.93	53.2	73.4
															52.6	69.4
12	19	4.44	0.47	2.24	0.63	1.61	2.30	2.93	4.54	50.6	64.3	— 6.0	31.6	2.60	49.3	78.7
															45.7	86.5
															63.6	65.0
13	16	4.41	0.41	1.80	0.90	0.90	3.18	4.08	4.98	63.8	81.9	+18.7	22.0	3.57	47.9	87.9
															47.3	81.1
14	28	5.17	0.34	1.68	0.50	1.18	2.09	2.59	3.77	55.4	68.7	+21.4	27.8	2.63	53.6	78.2
15	28	4.16	0.30	1.34	0.56	0.90	2.22	2.78	3.68	60.3	75.5	+20.0	25.4	2.96	56.0	76.1
				1.46											61.6	71.2
16	11	3.93	0.70	3.21	1.26	1.95	2.57	3.83	5.78	44.5	66.2	+16.8	21.3	3.59	40.0	96.2
17	20	4.53	0.27	1.45	0.70	0.75	1.95	2.65	3.40	57.3	77.9	+28.3	35.0	2.68	50.0	82.2
															49.6	92.2
18	..	....	....	0.87	....	....	....	....	....	....	....	....	....	....	63.1	62.8
Mean	17.2	4.43	0.47	2.35	0.90	1.55	2.27	3.15	4.70	48.5	67.5	+11.0	28.1	2.92	51.2	80.7

* All figures are averages from at least two determinations. Volumes are expressed at 37 C., prevailing barometric pressure and complete saturation with water vapor.

those of Ayerza, Solari and Berconsky,[14] Arrillaga, Berconsky and Taquini,[15] Houssay and Berconsky,[16] Berconsky [17] and Capdehourat [18] in cases of Ayerza's disease.

In a consideration of the reliability of the findings in regard to the composition of alveolar air secured in patients with pulmonary disease, technical difficulties and uneven distribution of the gases in the alveoli have to be discussed. Proper washing of the dead space is prevented sometimes by the small volume of the reserve air. We considered 500 cc. the minimum amount of gas necessary to wash the dead space. In some cases expiration was so slow that in order to exhale 500 cc. about four to five seconds were needed. As during this time oxygen is being consumed and carbon dioxide produced, the values obtained must differ from the true values. Duplicate determinations made the same morning may be markedly different according to the time at which the samples are taken and the depth and velocity of the expiration. Each value given in table 2 represents the average of several determinations.

In some patients of our series the composition of the alveolar air was investigated by serial sampling as described under "Methods." In order to compare normal persons with emphysematous subjects, the values of the first alveolar sample (taken when 500 cc. of air had been expired) and the last (taken six seconds after the beginning of expiration) were chosen. The results are summarized in table 3. It can be seen that in both groups the last sample has a lower oxygen and a higher carbon dioxide content than the first one, the difference being greater in emphysematous subjects. The average values for first and last samples were 0.30 volume per cent for oxygen and 0.57 volume per cent for carbon dioxide in the normal group and 0.99 and 2.10 volumes per cent for carbon dioxide and oxygen, respectively, in the emphysematous groups.

Since no important changes in metabolic rate were observed in the patients, these results indicated that in emphysematous lungs the alveolar air is unevenly distributed. The average alveolar respiratory quotients were 0.80 and 0.77 for the first and last samples from the normal

14. Ayerza, L.; Solari, L. A., and Berconsky, I.: Cianosis por hipoventilación alveolar en un "cardíaco negro" de Ayerza, Rev. Soc. de med. int. y Soc. de tisiol. **6**:511, 1930.

15. Arrillaga, F. C.; Berconsky, I., and Taquini, A. C.: Sindrome de hipoventilación alveolar, Rev. Asoc. méd. Argent. **6**:542, 1930.

16. Houssay, B. A., and Berconsky, I.: Cianosis por hipoventilación alveolar, Cong. nac. de med., Actas y trab., Buenos Aires **2**:91, 1932; Presse méd. **40**:1759, 1932.

17. Berconsky, I.: La función hemo-respiratoria en los "cardíacos negros de Ayerza," Semana méd. **1**:1569, 1933.

18. Capdehourat, E. L.: La cianosis de los cardiacos negros de Ayerza, Buenos Aires, Aniceto López, 1934.

persons and 0.75 and 0.68 for those from the patients with pulmonary disease. Since the respiratory quotients of the expired air were the same in both groups, these results indicate that the samples came from underventilated areas and that hypoventilation is more severe in the last sampled alveoli. These results confirm the findings of Sonne and Roelsen.

The uneven distribution of the gas in the alveoli of patients with pulmonary disease had been studied as early as 1911 by Siebeck [19] and

TABLE 3.—*Comparison Between Two Samples of Alveolar Air in Normal Persons and in Patients with Chronic Pulmonary Diseases* *

Subject	Alveolar CO_2, per Cent			Alveolar O_2, per Cent		
	First Sample	Last Sample	Difference	First Sample	Last Sample	Difference
Normal Subjects						
M. V.	5.69	6.20	0.51	14.00	13.69	0.31
	6.17	6.41	0.24	14.82	14.07	0.75
J. C. F.	4.55	5.05	0.50	16.34	15.61	0.73
	4.42	4.44	0.02	16.89	16.84	0.05
J. R. S.	5.86	6.25	0.39	12.31	11.16	1.15
	5.65	5.87	0.22	13.11	13.11	0.00
M. C.	5.68	5.84	0.16	13.30	12.58	0.72
	5.52	5.80	0.28	14.19	13.78	0.41
A. M.	3.46	3.86	0.40	17.08	16.25	0.83
	3.63	3.94	0.31	16.74	16.00	0.74
Mean	....	....	0.30	.....	.....	0.57
	Alveolar CO_2, per Cent			Alveolar O_2, per Cent		
Case	First Sample	Last Sample	Difference	First Sample	Last Sample	Difference
Emphysematous Patients						
4	6.29	6.80	0.51	12.68	11.49	1.19
	5.93	6.78	0.85	13.69	11.46	2.23
5	5.91	6.68	0.97	14.23	12.60	1.73
7	6.37	8.80	2.43	12.13	7.58	4.55
13	6.20	6.97	0.77	12.80	11.43	1.37
	6.47	6.63	0.16	12.54	11.37	1.17
15	8.16	8.72	0.56	11.38	9.97	1.41
19	7.52	9.19	1.67	11.49	8.01	3.18
Mean	....	....	0.99	.....	.....	2.1

* The first sample was taken after 500 cc. of gas had been exhaled and the last one six seconds after the beginning of the expiration.

more recently by Sonne (1934) [20] in patients with bronchial asthma and pulmonary emphysema. By fractional sampling of the alveolar air, Sonne showed that the alveolar oxygen and the respiratory quotient decrease more rapidly in these patients than in normal subjects. This

19. Siebeck, R.: Ueber den Gasaustausch zwischen der Aussenluft und den Alveolen: III. Die Lungenventilation beim Emphysem, Deutsches Arch. f. klin. Med. **102**:390, 1911.

20. Sonne, C.: Respiratory Air Exchange in the Lungs Under Normal and Pathological Conditions, Acta med. Scandinav., 1934, supp. 59, p. 348.

would indicate that the last portions of the exhaled gas come from poorly ventilated areas or from alveoli perfused with more than the normal amount of blood. Roelsen [21] confirmed these results. Allowing these patients to take a single breath of hydrogen, he showed that the inhalated gas mixed incompletely in the lung and that the last-exhaled fraction came from poorly ventilated alveoli.

Darling and others [22] studied the rate of removal of nitrogen from the lungs by means of oxygen inhalation and showed that 4 of 5 patients with emphysema exhibited a considerable degree of unequal mixing in the lungs.

Christie [13] compared the composition of alveolar samples obtained with the Haldane and Priestly method in normal and emphysematous subjects with that of samples obtained with an automatic sampler which collected a small amount of air at the end of each normal expiration. For normal subjects, the results of the two methods agreed fairly well, but great discrepancies were observed in regard to the patients with emphysema, the Haldane method giving higher values for carbon dioxide pressure. This clearly indicates that the difference between the composition of the alveolar air expired in a normal breath and the composition of reserve air is greater in patients with emphysema than in normal persons. Evidence of poor mixing in cases of emphysema has also been presented by Bruns,[23] Hoover and Taylor [24] and Weiss.[25]

The unequal distribution of the gas in the emphysematous lung is possibly greater than is indicated by the serial sampling because of the fact that only a small portion of the air in the lung can be investigated with this method. In case 15, for instance, only 200 cc. was exhaled between the first and the last sample in different proportions. Since the composition of the alveolar air depends on the amount of blood

21. Roelsen, E.: Fractional Analysis of Alveolar Air After Inspiration of Hydrogen as Method for Determination of Distribution of Inspired Air in Lungs: Examination of Normal Persons and Patients Suffering from Bronchial Asthma and Pulmonary Emphysema, Acta med. Scandinav. **95**:452, 1938; Composition of Alveolar Air Investigated by Fractional Sampling: Comparative Investigations on Normal Persons and Patients with Bronchial Asthma and Pulmonary Emphysema, ibid. **98**:141, 1939.

22. Darling, R. C.; Cournand, A., and Richards, D. W.: Studies on Intrapulmonary Mixture of Gases: V. Forms of Inadequate Ventilation in Normal and Emphysematous Lungs, Analyzed by Means of Breathing Pure Oxygen, J. Clin. Investigation **23**:55, 1944.

23. Bruns, O.: Die Bedeutung der spirometrischen Untersuchung von Emphysematikern und Herzkranken, Med. Klin. **6**:1524, 1910.

24. Hoover, C. F., and Taylor, L.: The Ventilatory Function of the Lung in Emphysema and Asthma, Arch. Int. Med. **15**:1 (Jan.) 1915.

25. Weiss, R.: Ueber der Durchmischungsverhältnisse in der Lunge bei der Bestimmung des zirkulatorischen Minutevolumens, Ztschr. f. d. ges. exper. Med. **61**:357, 1928.

perfusing the alveoli as well as on their ventilation, if the underventilated alveoli were also ischemic, hypoventilation would be underestimated with this method.

The conclusion can be drawn that in the emphysematous lung the composition of alveolar gases is not uniform on account of unequal ventilation. This condition makes the use of the term "alveolar air" incorrect, since there are several "alveolar airs," according to the portion of the lung sampled.

Pulmonary Ventilation.—Results are summarized in table 2. The average ventilation was 4.43 liters per square meter of body surface, with values ranging from 5.68 to 3.33. In a series of normal subjects the average ventilation was found to be 3.65, $\epsilon \pm 0.09$, liters per square meter. The difference between the averages was 0.780 ± 0.174, i.e., statistically significant. Robinson [8] has studied pulmonary ventilation in normal subjects of different ages. His data were recalculated for persons between 40 and 60 years and a value of about 4 liters per square meter of body surface obtained. This would indicate that in emphysema the pulmonary ventilation shows a tendency to increase, although in most cases the individual values are within the normal range. This is in accord with the findings of Scott,[26] Meakins and Davies,[12] Hoover,[27] Staehelin and Schütze [28] and others. On the other hand, Berconsky [17] found that pulmonary ventilation was definitely diminished in some of the patients studied by him. This appears clearly from the figures for carbon dioxide content of the expired air. However, the minute ventilation was increased in some of his patients. This slight tendency toward an increased ventilation in our cases is also reflected in the oxygen equivalent, which gives an average of 28.1, $\epsilon \pm 1.33$, as compared with 22.8, $\epsilon \pm 0.62$, in the normal group. The difference of 5.3 ± 1.47 is statistically significant. The carbon dioxide of the expired air was lowered by 2.92, $\epsilon \pm 0.117$, for the emphysematous group and by 3.75, $\epsilon \pm 0.09$, for a normal group. The difference of 0.810 ± 0.145 is significant.

This increased ventilation may be due to (*a*) cardiac decompensation or (*b*) asphyctic stimulus.

The first possibility cannot be ruled out in cases 12 and 15. On the other hand, the patients in cases 6 and 17, who had the highest oxygen equivalent and the lowest carbon dioxide content in the expired air, did not show any sign of heart failure. As will be considered later,

26. Scott, R. W.: Observations on the Pathologic Physiology of Chronic Pulmonary Emphysema, Arch. Int. Med. **26**:544 (Nov.) 1920.

27. Hoover, C. F.: The Alveolar Air and Minute Volume of Air in Pulmonary Emphysema, Tr. A. Amer. Physicians **27**:572, 1912.

28. Staehelin, R., and Schütze, A.: Spirographische Untersuchungen an Gesunden, Emphysematikern und Asthmatikern, Ztschr. f. klin. Med. **75**:15, 1912.

the effect of anoxia on ventilation was investigated by comparing the ventilation when the subject was breathing air and when he was breathing pure oxygen. The decrease observed in all cases but one indicates that anoxemia is an important factor in the observed hyperventilation.

Respiratory Rate.—As shown in table 2, the average respiratory rate was 17.2 respirations per minute. Rates of 15.5, 12.4 and 11.8 were found by Robinson in three groups of normal subjects of a mean age of 44, 52 and 63 years respectively. Conversely, for the tidal air the average value was 474 cc., lower than the values of Robinson [8] and those found in the normal group studied by us. Diminution of the tidal air has been found by Hoover,[27] Scott,[26] Houssay and Berconsky,[16] Christie,[15] Berconsky [17] and Capdehourat.[18]

When the composition of the alveolar air is compared with the pulmonary ventilation, one is struck by the fact that in spite of the slight hyperventilation the alveolar carbon dioxide is high and the oxygen low. The fact that in most of these cases the metabolic rate was normal indicates that the efficiency of the ventilation is decreased. Decrease of the tidal air, one of the conditions leading to poor ventilatory efficiency, was present in some cases, but in others the amount was normal. The ineffectiveness of ventilation in our cases must be explained by the unequal ventilation of the different parts of the lungs. As Sonne [20] pointed out, the fact that the alveolar respiratory quotients were lower than those found in expired air of the same subject suggests that in the first-evacuated alveoli the respiratory quotient must be higher. This effect could be produced if most of the alveoli evacuated at the beginning of expiration were hyperventilated and those evacuated toward the end hypoventilated. The hyperventilation of some areas will decrease the efficiency of the ventilation and simulate an increase in the respiratory dead space. In fact, if the dead space is considered as the amount of air in which the alveolar air has to be diluted to become expired air, the low carbon dioxide and high oxygen contents of the hyperventilated alveoli will increase the dead space beyond its anatomic limit. So the apparent dead space can be used as a measure of the difference between the composition of the deep alveolar air and that of air exhaled during a normal expiration, other things being equal. In both normal subjects and emphysematous patients a value similar to that for the effective dead space was calculated as follows: Ventilation and respiratory rate were measured during ten minute periods. At the end of these periods, alveolar air was taken as usual. Expired and alveolar air was analyzed, and from these values and the value for tidal air the dead space was calculated with the use of Bohr's formula. This has to be distinguished from the effective dead space calculated in the usual way. It approaches the effective dead space when the distribution of the gas in the lung approaches uniformity. The effective tidal air was obtained by subtract-

ing the dead space calculated in this way from the tidal air. The formula $\frac{\text{effective tidal air}}{\text{tidal air}} \times 100$ is a measure of the effectiveness of the removal of the gas in each breath. In table 4 the utilization of the tidal air in some of our patients is compared with that in normal subjects. It can be seen that in normal persons the utilization of the tidal air is about 60 per cent and in emphysematous persons 40 per cent. Berconsky [17] has made a similar calculation, subtracting from the tidal air the effective dead space as found by the usual method. He found that healthy persons utilize 73 per cent of the tidal air and patients with Ayerza's disease 46 per cent, values close to those found by us.

The diminished utilization of the tidal air shown in table 4 is due to two factors: (*a*) shallower breathing in the emphysematous group and (*b*) simulated increase of the dead space. In our cases the latter factor was the more important one.

TABLE 4.—*Effectiveness of Pulmonary Ventilation in Patients with Emphysema and in Normal Subjects*

Emphysema				Normal Persons			
		Effective Tidal Air,* per Cent				Effective Tidal Air, per Cent	
Case	Tidal Air, Cc.	CO_2	O_2	Subject	Tidal Air, Cc.	CO_2	O_2
4.....	530	48.7	44.9	J. D.....	446	53.8	53.0
8.....	558	37.8	37.8	J. C. F.....	610	66.0	61.8
10.....	573	39.6	29.3	C.....	495	59.0	61.2
13.....	414	40.3	30.9	J. R. E.....	938	73.8	69.0
15.....	276	36.6	35.1	M. I. C.....	495	60.5	62.0
17.....	278	38.5	35.6	D. G.....	511	57.0	56.0
Mean.....	438	40.2	35.6		582	61.7	60.5

* Effective tidal air was calculated by subtracting from the tidal air the apparent dead space (see text) calculated from CO_2 and O_2 values and expressing the result in percentage of the values for tidal air.

In the preceding discussion it was assumed that the increased dead space was simulated by the uneven distribution of the gas in the lung. As a matter of fact, similar results can be obtained if the anatomic dead space has increased. By serial sampling of the expired air, Christie and Loomis have tried to differentiate between a true increase of the dead space and the one simulated by the shunting of air into relatively ischemic alveoli. They did not find evidence of any true increase in the anatomic or physiologic dead space. Berconsky [17] investigated the respiratory dead space in 10 cases of Ayerza's disease and found a mean value of 132, as compared with 171 found in normal subjects. As he pointed out, this is probably due to the diminution of tidal air. However, his results, as well as those obtained by Capdehourat,[18] cannot be considered as conclusive on account of difficulties in getting true alveolar samples in these patients. The results obtained by Berconsky

showed that in spite of the diminution of the dead space the ratio of dead space to tidal air increased in his cases, which indicated that shallow breathing was the most important source of alveolar hypoventilation.

We can summarize the facts as follows: The ventilation is slightly increased in these patients, but on account of the unequal ventilation of the alveoli and the decreased tidal air, the efficiency is low. This inefficient ventilation is responsible for the fact that despite the slight increase in the respiratory minute volume the alveolar gases have a higher carbon dioxide and a lower oxygen content than normal.

The Lung Volume and Its Subdivisions.—The results are summarized in table 2.

Absolute Values.—Vital capacity was found to be diminished, extreme values being 0.87 and 3.81 liters, with an average of 2.35. Only 5 of 15 patients had values above 2.6 liters, the lowest normal figure found by Kaltreider and others [29] in healthy males of similar age, and only 2 had values above 3.45 liters, the lowest value found by Robinson [8] in age groups VII, VIII and IX, which correspond to our group.

The spirograms frequently showed the failure of the respiration to return rapidly to the previous level after a deep inspiration or expiration.

The decrease of the vital capactiy seemed to be due to a reduction in complemental air (mean value, 1.55 liters), reserve air being maintained at about normal (mean value, 0.90 liter).

Tidal air will be considered later in relation to dead space and effective ventilation.

The residual air ranged between 1.00 and 3.18 liters, with an average of 2.27 liters. The figures are higher than those found by Kaltreider and others and by Robinson in normal men (0.54 to 2.29, with an average of 1.30 liters, and 0.66 to 2.39, with an average of 1.67 liters).

Functional residual air (midcapacity) ranged between 1.80 and 4.10 liters with a mean value of 3.15, being increased in several cases as compared with the standards of Kaltreider and others [29] and Robinson [8] (1.09 to 3.05, with an average of 2.00, and 1.27 to 3.46, with an average of 2.39, respectively).

Total pulmonary capacity varied within normal limits when compared with Kaltreider's standards (3.62 to 7.61 liters), and it was diminished in 4 male subjects when compared with Robinson's (4.34 to 7.90 liters). The average in our series, 4.70 liters, was smaller than that in both series of normal subjects (5.37 and 5.95 liters).

Relative Values.—The wide normal range makes the absolute value a doubtful index in judging abnormalities of these functions. Therefore, results expressed as percentage of the total capacity are also considered

29. Kaltreider, N. L.; Fray, W. W., and Hyde, H. V.: The Effect of Age on the Total Pulmonary Capacity and Its Subdivisions, Am. Rev. Tuberc. **37**:662, 1938.

in the chart. The mean value for the relation of residual air to total capacity was 48.5 per cent, extreme values being 26.3 and 63.8, a significant increase when compared with Kaltreider's and Robinson's figures (average, 24.5 and 27.8 per cent respectively). In cases 3, 4 and 11 the levels fell within normal range. On the other hand, when the relation of functional residual air to total capacity was considered, there were increased values in all cases except case 11, the mean being 67.5 per cent.

These results agree with those obtained by Anthony,[30] Hurtado and others,[31] Christie [13] and Kaltreider and others [32] in cases of pulmonary fibrosis and emphysema and with those of Berconsky [17] in cases of Ayerza's syndrome.

Individual differences found in our series can be explained on the basis of the prevalent emphysema or fibrosis of the lungs. However, heart failure may influence the decrease in the vital capacity and total capacity of patients with Ayerza's disease.

No significant correlation was found in our cases between absolute or relative values of residual air or functional residual air and arterial oxygen saturation or alveolar air tensions.

Basal Metabolic Rate.—Determinations of the basal metabolic rate were made on 14 patients. The rates were normal in half of them and moderately high in the other half. Metabolism in patients with Ayerza's disease has been studied by Berconsky [17] who found slight increase in 5 of 7 cases and ascribed it to the presence of heart failure. In our group of 7 patients with normal metabolism 3 had heart failure and the other 4 had no sign of cardiac involvement.

Among the 7 patients with increased metabolic rate, 4 had cardiac failure and 3 had not.

These results indicate that besides cardiac failure other factors such as respiratory dyspnea may cause an increase of metabolism in patients with chronic pulmonary disease.

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30. Anthony, A. J.: Untersuchungen über Lungenvolumina und Lungventilation, Deutsches Arch. f. klin. Med. **167**:129, 1930.

31. Hurtado, A.; Fray, W. W., and McCann, W. S.: Studies of Total Pulmonary Capacity and Its Subdivisions: IV. Preliminary Observations on Cases of Pulmonary Emphysema and of Pneumoconiosis, J. Clin. Investigation **12**:833, 1933. Hurtado, A.; Kaltreider, N. L.; Fray, W. W.; Brooks, W. D. W., and McCann, W. S.: Studies of Total Pulmonary Capacity and Its Subdivisions: VI. Observations on Cases of Obstructive Pulmonary Emphysema, ibid. **13**:1027, 1934; VIII. Observations on Cases of Pulmonary Fibrosis, ibid. **14**:81, 1935.

32. Kaltreider, N. L.; Fray, W. W., and Hyde, H. V.: Further Studies of the Total Pulmonary Capacity and Its Subdivisions in Cases of Pulmonary Fibrosis, J. Indust. Hyg. & Toxicol. **19**:163, 1937.

BLOOD.—*Oxyhemoglobin Dissociation Curve.*—In 5 cases of Ayerza's syndrome four points on the oxygen dissociation curve of the arterial blood at 37 C. and p_H 7.40 were secured. All the patients had severe anoxia, arterial oxygen tension ranging between 37 and 53 mm. of mercury and oxyhemoglobin capacity between 25.96 and 30 volumes per cent. The values of the oxygen pressure at half saturation, at $(p_H)_S$ 7.40 and at arterial $(p_H)_S$ are given in table 5. It can be seen that the average oxygen tension at half saturation, 25.8 mm. of mercury, does not differ appreciably from the values obtained in normal persons at sea level. On the other hand, as the arterial $(p_H)_S$ of the group with Ayerza's disease is lower than that of the normal group, the curve at the arterial $(p_H)_S$ is displaced to the right, and oxygen pressure for hemoglobin, or oxyhemoglobin, is increased. These findings suggest that the hemoglobin has not changed in this type of anoxemia.

TABLE 5.—*Position of the Oxygen Dissociation Curve in Patients with Ayerza's Syndrome*

Case	pO_2 for Hb = HbO_2 Mm. Hg *	
	$(pH)_S$ 7.40	Arterial pH
2	25.5	28.5
4	25.0	27
10	27.5	29
12	24.5	26
15	26.5	29
Mean	25.8	27.9

*Values for pO_2 at half saturation are at 37 C. for constant $(pH)_S$ 7.40 and for the pH of the arterial blood as drawn.

Oxyhemoglobin dissociation curves were studied in 2 cases of emphysema by Meakins and Davies,[12] and no appreciable deviation from normal was observed. The position of the dissociation curve at high altitude has been investigated by Barcroft and others,[33] Buikov and Martinson,[34] Dill and others,[35] Keys and his associates [36] and, more

33. Barcroft, J., and others: Observations Upon the Effect of High Altitudes on the Physiological Processes of the Human Body, Carried Out in the Peruvian Andes, Chiefly at Cerro de Pasco, Phil. Tr. Roy. Soc., London, s. B. **211**:351, 1923.

34. Buikov, K. M., and Martinson, E. E.: Arkh. sc. biol. (USSR) **33**:147, 1933, cited by Aste-Salazar and Hurtado.[37]

35. Dill, D. B.; Edwards, H. T.; Folling, A.; Oberg, S. A.; Pappenheimer, A. M., and Talbott, J. H.: Adaptations of the Organism to Changes in Oxygen Pressure: Physicochemical Changes in Human Body at Low Oxygen Pressure, J. Physiol. **71**:47, 1931.

36. Keys, A.; Hall, F. G., and Barron, E. S. G.: The Position of the Oxygen Dissociation Curve of Human Blood at High Altitude, Am. J. Physiol. **115**:292, 1936.

recently, Aste-Salazar and Hurtado.[37] The last-named authors were able to show a slight shift of the curve to the right, confirming the previous work of Keys and others.

Oxygen Capacity of the Blood.—Our results are summarized in table 7. It can be seen that in most cases the oxygen capacity is well above the normal range.

The oxygen capacity of the blood in cases of emphysema has been investigated by Meakins,[38] Campbell, Hunt and Poulton,[39] Himwich and Loebel,[40] Kountz, Alexander and Dowell [41] and Christie.[13] The values were within the normal limits in most cases but increased in some. Hurtado, Kaltreider and McCann [42] studied 24 cases of emphysema and 37 cases of pulmonary fibrosis. The oxygen capacity of the blood was markedly increased in only 9 cases and was normal in the others. Kaltreider, Hurtado and Brooks [43] found 16.2 Gm. of hemoglobin per hundred cubic centimeters in a group of emphysematous patients and an average of 16.6 Gm. in fibrotic patients as compared with 16.2 Gm. of hemoglobin as the average value in a normal group.

The oxygen capacity of the blood in patients with Ayerza's syndrome has been investigated by Ayerza, Solari and Berconsky,[14] Arrillaga, Berconsky and Taquini,[15] Houssay and Berconsky [16] and Capdehourat.[18] Berconsky [17] found a mean value of 27.30 volumes per cent, with extremes ranging from 22.09 to 33.54.

Case 4 deserves special discussion. In the first determination a high oxygen capacity was found (30 volumes per cent), if one considered the relatively high arterial saturation and oxygen pressure. A month later the patient showed a much lower oxygen capacity (26.3 volumes), with only a small change in arterial oxygen saturation and pressure.

37. Aste-Salazar, H., and Hurtado, A.: The Affinity of Hemoglobin for Oxygen at Sea Level and at High Altitudes, Am. J. Physiol. **142**:733, 1944.

38. Meakins, J. C.: Gases in Human Arterial Blood in Certain Pathological Pulmonary Conditions, and Their Treatment with Oxygen, J. Path. & Bact. **24**:79, 1921.

39. Campbell, J. M. H.; Hunt, G. H., and Poulton, E. P.: An Examination of the Blood Gases and Respiration in Disease, with Reference to the Cause of Breathlessness and Cyanosis, J. Path. & Bact. **26**:234, 1923.

40. Himwich, H. E., and Loebel, R. O.: The Oxygen Saturation of Hemoglobin in the Arterial Blood of Exercising Patients, J. Clin. Investigation **5**:113, 1927.

41. Kountz, W. B.; Alexander, H. L., and Dowell, D.: Emphysema Simulating Cardiac Decompensation, J. A. M. A. **93**:1369 (Nov. 2) 1929.

42. Hurtado, A.; Kaltreider, N. L., and McCann, W. S.: Studies of Total Pulmonary Capacity and Its Subdivisions: IX. Relationship to the Oxygen Saturation and Carbon Dioxide Content of the Arterial Blood, J. Clin. Investigation **14**:94, 1935.

43. Kaltreider, N. L.; Hurtado, A., and Brooks, W. D. W.: Study of the Blood in Chronic Respiratory Disease, with Special Reference to the Volume of the Blood, J. Clin. Investigation **13**:999, 1934.

We believe that the patient had had a period of severe anoxemia, with a corresponding increase of the hemoglobin capacity, and had improved before being admitted to the service. When the determinations were carried out, the arterial saturation was higher but the hemoglobin capacity had not yet reached a new value in accordance with the improved oxygenation of the blood. In cases 17 and 18 the oxygen capacity was low, notwithstanding the severe anoxia; the patients in these cases were the only two females in our series.

In order to compare our data with those obtained by Hurtado, Merino and Delgado [44] at high altitude, our patients were classified into two groups, those with arterial saturation above 80 per cent and those with saturation below 80 per cent. In the Ayerza group with an arterial saturation of 86.4 ± 0.63 volumes per cent, a hemoglobin content of 18.82 ± 0.91 Gm. per hundred cubic centimeters was obtained, as compared with 87.6 ± 0.27 and 18.82 ± 0.15 obtained by Hurtado and others in native residents at an altitude of 3,730 meters. In the group with lower saturation the figures were 74.7 ± 2.04 volumes per cent and 20.1 ± 0.17 Gm. of hemoglobin for the Ayerza group and 81.4 ± 0.45 volumes per cent and 20.76 ± 0.20 Gm. for the residents at 4,540 meters.

This shows that in patients with pulmonary disease a coarse correlation exists between the degree of the anoxia and the response of the bone marrow and that this response was less in our second group than in persons at high altitude. This difference may be explained by the finding of Hurtado and others [44] that when the arterial saturation reaches a value of about 60 to 70 per cent there is a decrease rather than a further increase in the hemoglobin content and the red blood cell count.

The question arises why in most cases of anoxemia due to pulmonary changes the polycythemic response tends to be less than when there are corresponding degrees of arterial oxygen unsaturation at high altitude, as pointed out by Hurtado and his co-workers. This may be due, in part at least, to the fact that in many pulmonary diseases the anoxic stimulus is variable, depending on the degree of the bronchial spasms, or to other factors.

We believe that these results support the view that the anoxic stimulation is the only cause of the increase in hemoglobin found in this disease.

Hematocrit Readings.—To calculate the hemoglobin concentration per volume of red cells, hematocrit readings were made on the same sample of arterial blood in which the hemoglobin content was determined gasometrically. The results presented in table 6 are compared with those obtained in normal subjects at sea level or at high altitude and in patients with pulmonary fibrosis and emphysema. It can be seen that

44. Hurtado, A.; Merino, C., and Delgado, E.: Influence of Anoxemia on the Hemopoietic Activity, Arch. Int. Med. **75**:284 (May) 1945.

the hemoglobin content per hundred cubic centimeters of red cells is lower in our patients. The group at high altitude, in which the hemoglobin content of the blood is similar to that in our group, has an average hemoglobin concentration of 34.6 Gm. per hundred cubic centimeters of cells, as compared with 29.3 in our cases. This difference is too great to be explained by the water shift produced by the increased

TABLE 6.—*Values for Hematocrit, Hemoglobin and Hemoglobin to Hematocrit Ratio in Normal Persons at Sea Level and at High Altitude and in Patients with Pulmonary Disease*

Case	Hematocrit, Volume, per Cent	Hemoglobin, Gm./100 Cc.	Hemoglobin to Hematocrit, per Cent
A			
2	61.9	18.82	30.4
4	70.4	22.10	31.4
	62.84	18.90	30.3
10	70.5	20.80	29.5
	66.8	19.84	29.7
12	67.7	20.15	29.8
13	70.1	19.6	28.0
15	69.9	20.1	28.8
	70.6	20.4	28.9
Mean	68.6	20.08	29.30
B			
Normal Persons at Sea Level			
Hurtado and others [44]	46.8	16	34.2
Kaltreider and others [43]	45.1	16.2	35.9
Haden, R. L.: Folia haemat. **31**: 113, 1925	45	15.23	33.9
Altitude (4,540 M.)			
Hurtado and others [44]	59.9	20.76	34.6
Emphysema			
Kaltreider and others [43]	46.3	16.2	35.0
Fibrosis			
Kaltreider and others [43]	49.7	16.6	33.4
Ayerza's Syndrome			
Author's data	68.6	20.08	29.30

In table A are the individual values of some of our patients, and in table B our average value was compared with those reported in the literature for normal persons at sea level and at high altitude and for patients with emphysema and fibrosis.

carbon dioxide tension of the arterial blood in the patients at high altitude. It is possible that the slight acidosis present in our patients could impair the production of hemoglobin by the bone marrow. The results obtained in 3 patients with morbus caeruleus point in the same direction. In 2 of them, with a normal arterial $(p_H)_S$, the hemoglobin values per hundred cubic centimeters of red cells were 33.2 and 31.8, and in the other, with an arterial $(p_H)_S$ of 7.30, values of 28.5 and 29.60 were secured. However, we realize that these results are far from con-

clusive and that other factors, such as poor general condition and infections, can be important.

Oxygen Saturation and Content of the Arterial Blood.—Table 7 shows that in our cases the average oxyhemoglobin content of arterial blood was 20.44 volumes per cent. The patients in cases 17 and 18 have been excluded because they were emphysematous anoxemic women without polycythemia. The value is higher than that of 19.50 ± 0.16 found by Hurtado, Kaltreider and McCann [42] in cases of pulmonary fibrosis and that of 18.75 ± 0.27 found by the same authors in cases of emphysema.

TABLE 7.—*Characteristics of the Arterial and Equilibrated Blood of Patients with Pulmonary Disease*

Case	Arterial pO_2, Mm. Hg	Arterial HbO_2, per Cent	Arterial HbO_2, Volumes per Cent	HbO_2 Capacity, Volumes per Cent	Arterial pCO_2, Mm. Hg	Arterial Total $(CO_2)_b$, Volumes per Cent	$(T40)_b$,* Volumes per Cent	$(T40)_s$, Volumes per Cent	Arterial (p_H)
1	50.0	85.4	22.24	26.04	52.0	52.60	45	57.2	7.33
2	44.5	79.9	20.73	25.96	64.8	63.89	51.0	64.6	7.32
3	57.5	87.5	21.75	24.84	53.0	50.12	43.1	53.7	7.30
4	53.0	87.4	26.23	30.00	49.0	51.30	44.5	57.9	7.36
	52.0	84.2	21.30	25.92	65.0	63.30	49.8	62.8	7.31
5	55.0	88.4	18.86	21.35	59.5	59.95	50.7	61.7	7.32
6	53.0	87.8	20.90	23.80	46.0	49.27	45.2	55.8	7.36
7	49.0	84.2	18.82	22.35	56.0	57.60	48.2	59.2	7.33
8	57.5	86.7	20.46	23.59	55.0	56.28	48.3	60.7	7.33
	50.5	81.4	18.74	23.00	62.0	64.65	62.9	66.3	7.34
9	45.0	81.2	18.70	22.90	56.0	62.00	52.6	65.2	7.37
10	45.2	77.3	21.56	27.87	52.0	53.10	45.1	57.7	7.34
	43.5	75.4	20.03	26.57	45.2	44.90	40.4	50.6	7.33
12	40.3	79.2	21.25	26.83	55.0	58.30	49.3	63.0	7.36
13	36.0	71.0	18.64	26.23	58.3	65.78	53.8	69.3	7.39
	44.5	80.0	21.60	27.00	63.6	62.10	49.0	63.0	7.32
15	37.0	66.4	17.86	26.90	70.0	65.10	49.2	63.2	7.29
	38.6	68.6	18.72	27.32	67.2	64.28	48.5	62.1	7.30
17	55.0	86.1	14.25	16.55	62.0	62.24	53.4	63.2	7.30
18	42.5	82.7	12.88	15.57	50.0	62.65	58.00	68.2	7.41
Mean	47.94	81.75	20.44 ± 0.47	25.07	56.61	57.7	48.17 ± 0.93	60.55 ± 1.22	7.33

* $(T40)^b$ means total carbon dioxide content of the blood equilibrated at 40 mm. of mercury of carbon dioxide pressure and complete saturation. $(T40)_s$ is the corresponding value in plasma or serum.

The differences are significant in both instances. In a recalculation of the data of Robinson [8] on normal men between 40 and 60 years, an average value of 19 volumes of oxygen per cent in arterial blood was obtained. Dill, Edwards and Consolazio [45] found an average oxygen content of arterial blood of 19.15 volumes per cent in 12 normal men aged 23 to 45. These results show that in Ayerza's syndrome the

45. Dill, D. B.; Edwards, H. T., and Consolazio, W. V.: Blood as a Physicochemical System: XI. Man at Rest, J. Biol. Chem. **118**:635, 1937.

oxygen content of the arterial blood is slightly increased. They are in accordance with the findings of Berconsky, who in 8 cases of Ayerza's syndrome found a mean value of 21.15 volumes per cent of oxygen in arterial blood. A similar increase has been found at high altitude by Talbott and Dill [46] in healthy workmen living at 17,500 feet, with an average of 22.54 volumes per cent.

As found by all the workers in this field, the oxygen saturation was below the normal figure in all cases, the values ranging from 88.4 to 66.4 per cent. In healthy subjects between 40 and 60 years Robinson [8] found an average saturation of 93 per cent, extreme values being 90 and 97 per cent. The recent work of Roughton and others [47] questioned the validity of the calculation of arterial oxygen saturation with the tonometer technic. However, since we have employed the same method as Robinson, both values can be compared. Moreover, if it is admitted that the oxyhemoglobin capacity obtained by this method is about 2 per cent too high, as calculated by Roughton and others,[47] our saturation values will be only about 1.5 per cent too low.

Arterial Oxygen Pressure.—The oxygen pressure in the arterial blood was calculated from the oxygen dissociation curve and the arterial saturation. In cases in which no dissociation curve was made, arterial oxygen pressure was obtained with the use of a standard curve brought to the arterial p_H of the patient. As in most cases the arterial oxygen saturation was below 85 per cent; the error introduced by underestimating the saturation in the amount calculated by Roughton and others [47] is practically unimportant. In the remainder of the cases (86 to 88.4 per cent saturation) the estimated arterial oxygen pressure will be only about 3 to 4 mm. of mercury too low.

The results are summarized in table 7. It is shown that oxygen pressure was below the normal value in all cases.

Arterial Carbon Dioxide and p_H.—The alkaline reserve (T 40)$_b$, defined as the volumes of carbon dioxide per hundred cubic centimeters of oxygenated blood at a carbon dioxide pressure of 40 mm. of mercury, was found to be within the normal range in almost every case (table 7). The average was 48.17 volumes, close to the values for normal persons reported in the literature, which include a mean of 48 volumes in the basal arterial blood of 12 men reported on by Dill, Edwards and Consolazio [45] and means ranging from 47.2 to 49.4 volumes reported by Robinson [8] in healthy subjects from 25 to 80 years old. The average

46. Talbott, J. H., and Dill, D. B.: Clinical Observations at High Altitude: Observations on Six Healthy Persons Living at 17,500 Feet and Report of One Case of Chronic Mountain Sickness, Am. J. M. Sc. **192**:626, 1936.

47. Roughton, F. J. W.; Darling, R. C., and Root, W. S.: Factors Affecting the Determination of Oxygen Capacity Content and Pressure in Human Arterial Blood, Am. J. Physiol. **142**:708, 1944.

alkaline reserve of the plasma, $(T40)_a$,[48] was 60.55 volumes of oxygen per cent, higher than the value of 58 volumes found by Dill, Edwards and Consolazio.[45] The alkaline reserve is increased in plasma but not in whole blood because of the fact that the increased red cell volume (in which the carbon dioxide content is lower than in the plasma) decreases the carbon dioxide content of the total blood.

In case 12 four points on the carbon dioxide dissociation curve of arterial blood at 37 C. and complete saturation were determined. The curve was steeper than that in normal persons because of the high hemoglobin content of the blood, but it was in agreement with that calculated according to the nomogram of Henderson and others [1] from the alkaline reserve and the hemoglobin capacity. As Henderson's nomogram has been constructed from data obtained on normal persons, the results suggest that no change in the oxyhemoglobin base–binding properties has occurred.

The mean value of total carbon dioxide content of the arterial blood, $(TCO_2)_b$, was 57.7 volumes per cent, higher than the means varying from 49.2 to 51.6 volumes found by Robinson [8] in his adult groups, that of 48.6 found by Dill, Edwards and Consolazio [45] in 12 normal men studied under basal conditions and that of 49.9 found by Looney and Jellinek [49] in 25 normal male subjects. This increase in $(TCO_2)_b$ of the arterial blood confirms the results obtained by Berconsky (1933) in cases of Ayerza's syndrome.

Scott,[26] Meakins and Davies [12] and Dautrebande [50] found that in emphysema there is an increase in the carbon dioxide content of the arterial blood and Hurtado, Kaltreider and McCann [42] that the carbon dioxide content of arterial blood was increased chiefly in cases of emphysema but not in cases of pulmonary fibrosis.

The carbon dioxide pressure of the arterial blood has been calculated as explained under "Methods." Our mean value of 56.6 mm. of mercury is higher than the 43 mm. obtained by Robinson in healthy adults aged between 40 and 60 and the 41 mm. obtained by Dill, Edwards and Consolazio [45] in younger subjects. In our series, the values in all cases but 3 are over 50 mm., which can be taken as the upper normal limit for subjects of the same age, according to Robinson's data.[8] When the carbon dioxide pressure of arterial blood was compared with its oxygen

48. The carbon dioxide content of the plasma was calculated from $(T40)_b$ and the hemoglobin capacity with the cartesian nomogram of Henderson and others.[1]

49. Looney, J. M., and Jellinek, E. M.: The Oxygen and Carbon Dioxide Content of the Arterial and Venous Blood of Normal Subjects, Am. J. Physiol. **118**:225, 1937.

50. Dautrebande, L.: L'équilibre acide-base chez les emphysémateux: Ses variations au cours de la décompensation cardiaque, Compt. rend. Soc. de biol. **93**:1025, 1925.

pressure or hemoglobin saturation, a poor correlation was found. However, the patients with highest arterial carbon dioxide pressure were those in whom oxygen saturation reached its lowest values.

The p_H of arterial serum ranged from 7.29 to 7.39, with an average value of 7.33, lower than the means of 7.37 to 7.42 found by Robinson in the various age groups. The lowest occurred in men between 48 and 55, 7.33 and 7.45 being the extreme values in the whole series of his subjects. These values compare closely with those obtained by others, i.e., Mori,[51] 7.40 to 7.42 in the various decades between the ages of 15 to 68; Shock and Hastings,[52] 7.40 in capillary blood in 39 normal men, and Dill, Edwards and Consolazio,[45] 7.40 in arterial blood of 12 normal men under basal conditions (range, 7.35 to 7.44).

From the previous data the conclusion can be drawn that primary carbon dioxide excess exists in the presence of chronic pulmonary insufficiency, partially compensated by the increase in the plasma bicarbonates.

TABLE 8.—*Distribution of Water, Combined Carbon Dioxide, Chloride and Hydrogen in Oxygenated Blood*

Case	$(H_2O)_s$, Gm./Cc.	$(H_2O)_c$, Gm./Cc.	$(Cl)_s$, mEq.	$(Cl)_c$, mEq.	^rCl	$(BHCO_3)_s$, mEq.	$(BHCO_3)_c$, mEq.	$^rHCO_3$	$(p_H)_s$	$(p_H)_c$	^rH
2	0.930	0.740	....	....	....	29.01	19.35	0.839	7.39	7.21	0.53
10	0.932	0.742	....	....	....	25.31	16.98	0.842	7.40	7.22	0.53
15	0.926	0.745	99.3	51.9	0.650	30.01	18.53	0.768	7.41	7.19	0.48

Arterial blood was equilibrated in a tonometer at a pO_2 of 190 mm. of mercury and to a pCO_2 necessary to get a p_H close to 7.40.

Distribution of Water and Electrolytes in Serum and Cells.—In 3 of the most severe cases, water, bicarbonate, p_H and chlorides were determined in red cells and plasma. The results are summarized in table 8.

Water content per liter of red cells $(H_2O)_c$ ranged between 740 and 745, compared with the mean value of 720, extremes being 714 and 732, obtained in 12 healthy men by Dill, Edwards and Consolazio.[45] Water serum values $(H_2O)_s$ ranged between 926 and 932, compared with the mean value of 938, with a range of 936 to 941, obtained by Dill and others. Notwithstanding the small number of our cases, we believe that on account of the slight dispersion of the values and the lack of

51. Mori, Z.: Age and Muscular Exercise, Jap. J. M. Sc., III, Biophysics **3**:309. 1936, cited by Robinson.[8]

52. Shock, N. W., and Hastings, A. B.: Studies of the Acid-Base Balance of the Blood: III. Variation in Acid-Base Balance of the Blood in Normal Individuals, J. Biol. Chem. **104**:585, 1934.

overlapping the differences found can be considered significant. The higher water content of the red cells keeps pace with the finding, mentioned previously, that the hemoglobin content per volume of red cells is diminished in these patients.

The bicarbonates in the cells and serum were increased, and their distribution in the fully oxygenated arterial blood at p_H 7.40 fell within the values given by Dill and others for normal persons.

As expected, the chlorides in the serum and cells were diminished in the only determination made, the distribution being near the normal value.

The distribution of hydrogen was about 0.50, lower than the averages found in smoothed curve of Dill and others.[45]

Hemorespiratory Exchanges.—In table 9 the oxygen and carbon dioxide pressures of arterial blood have been compared with the corresponding pressures in alveolar air. It can be seen that the arterial oxygen pressure is in every case lower than the alveolar one, differences ranging from 10.3 to 53.8, with an average of 30.7 mm. of mercury. In resting normal subjects at sea level the alveolar oxygen difference, ΔpO_2, estimated with the same method as we have employed, is about 20 mm. of mercury. However, Roughton and others [47] have shown that this difference is produced by systematic error in the calculation of the arterial oxygen pressure and that a nearly perfect equilibrium between alveolar and arterial gases does exist in normal subjects. Nevertheless when the saturation of arterial blood is below 85 per cent, the form of the oxygen dissociation curve makes the error in the calculation of the arterial oxygen pressure negligible and consequently difference in alveolar oxygen pressure practically disappears. For that reason, we will compare the values for alveolar oxygen difference in our patients with those obtained with the same method in healthy men at high altitude having a similar oxygen saturation.

At an altitude of 4,700 meters, with a mean arterial oxyhemoglobin of 78 per cent, Dill, Christensen and Edwards [53] found an average alveolar oxygen difference of + 3.4 mm. of mercury, extreme values being + 8.2 and — 1.3. If one considered 8.2 the upper normal limit, alveolar oxygen difference was increased in all our patients.

The alveolar carbon dioxide difference in healthy subjects aged 40 to 60 years was found to be about + 2 mm. of mercury by Robinson, extreme values ranging from — 5 to + 7 mm. In our cases (table 9) the mean alveolar carbon dioxide difference was + 3.4 mm., values ranging from — 14.4 to + 13.1, indicating a small increase in carbon dioxide pressure but a greater scattering of the values.

53. Dill, D. B.; Christensen, E. H., and Edwards, H. T.: Gas Equilibria in the Lungs at High Altitudes, Am. J. Physiol. **115**:530, 1936.

In discussing the mechanism by which the differences between the alveolar and arterial blood gases are produced, several possibilities must be considered.

A. Impairment of Gas Diffusion Through the Alveolar Wall. The fact that alveolar carbon dioxide difference is smaller than alveolar oxygen difference favors the hypothesis that an impairment in the alveolar permeability may exist; this being so, the former could be calculated from the latter. However, the considerable spread of the figures for alveolar carbon dioxide difference prevents closer analysis. On the other hand, the mathematical analysis of the diffusion of gases through the lung does not support the hypothesis previously mentioned.

TABLE 9.—*Relation Between Arterial and Alveolar Carbon Dioxide and Oxygen Pressure in Patients with Emphysema and Fibrosis of the Lung*

Case	pO_2 in Millimeters of Mercury			pCO_2 in Millimeters of Mercury		
	Alveolar	Arterial	Difference*	Alveolar	Arterial	Difference
2	63.0	45.6	17.4	62.1	72.0	— 9.9
	61.1	44.5	16.6	63.8	64.8	— 1.0
3	98.5	57.5	41.0	38.6	53.0	—14.4
4	92.5	53.0	39.5	46.8	49.0	— 2.2
6	95.5	53.0	42.5	41.4	46.0	— 4.6
7	60.6	49.0	11.6	63.6	56.0	+ 7.6
8	67.8	57.5	10.3	63.9	55.0	+ 8.9
	72.6	50.5	22.1	61.4	62.0	— 0.6
10	91.0	45.2	45.8	40.8	52.0	—11.2
	97.0	43.5	53.5	38.2	45.2	— 7.0
12	78.7	40.3	38.4	49.3	55.0	— 6.3
13	87.9	35.0	52.9	47.9	58.3	—10.4
	65.0	44.5	20.5	63.6	63.6	0
15	71.2	38.6	32.6	61.6	67.2	— 5.6
17	82.9	55.0	27.2	50.0	62.0	—12.0
18	62.8	42.5	20.3	63.1	50.0	+13.1
Mean	77.95	47.20	30.75	53.50	56.94	— 3.44

* The difference was calculated by subtracting the values for the pressure of the gases in the arterial blood from the corresponding values in the alveolar air.

The amount of oxygen diffusing through the lung in a given time can be obtained by the following expression: $O_2 = K \int_{t'}^{t} (P_a - P_b)\,dt$ in which O_2 indicates amount of oxygen diffusing, K diffusion constant and P_a and P_b alveolar and blood oxygen pressure. The alveolar oxygen pressure can be considered as constant, but the oxygen pressure of the blood changes from venous to arterial. In order to integrate $(P_a - P_b)$, $P_b\,(f)\,t$ must be known, but as a first approximation the mean values between alveolar and arterial pressure can be used. If venous oxygen pressure is taken to be 20 mm. of mercury and arterial oxygen pressure 47 mm., the mean will be 35.5 mm. and $(P_a - P_b)$ will be 78 — 33.5, or 44.5 mm.

If the differences between alveolar and arterial gases depend on generalized impairment of the diffusion process, 44.5 mm. of mercury has to be considered as a diffusion gradient, then

$$O_2 = K\ (44.5)$$

As the data were obtained on patients at rest, the basal oxygen consumption, for example, 250 cc., has to be transferred through the lung with a head of pressure of 44.5 mm. of mercury.

In order to increase the oxygen diffusion, K being constant, a corresponding increase in the diffusion gradient must occur; for instance, if 250 cc. of oxygen per minute passes through the lung with a head of pressure of 44.5 mm. of mercury for passing 500 cc. per minute, a head of pressure of 89 mm. of mercury needs to be postulated. Since this figure is higher than the average alveolar oxygen pressure, the results will indicate that most of these patients could not duplicate their basal metabolic rate, even when blood oxygen pressure would be zero. Although we did not study our patients under exercise, the data of Kaltreider and McCann [54] obtained on patients with considerable emphysema indicate that during exercise the oxygen consumption was about 700 to 800 cc. per minute and the arterial oxygen saturation did not fall below 85 per cent. This makes it problematic that alveolar oxygen difference can be due to a generalized diffusion impairment. Krogh,[55] studying the diffusion coefficients in cases of emphysema with the use of the carbon monoxide method, was unable to detect significant differences in normal persons. Further evidence against considering alveolar oxygen difference as a diffusion gradient will be presented later.

B. Uneven Distribution of the Gases in the Lungs: Under "Alveolar Air" evidence has been presented for uneven distribution of the gases in the lungs. In order to compare arterial and alveolar pressures, alveolar samples taken four seconds after the beginning of the expiration were used; in some cases better concordance could be found with subsequent samples. It is possible that in most cases the residual air may have a lower oxygen and a higher carbon dioxide content than what we accepted as the "alveolar sample." If the "alveolar sample" averaged the composition of the most and least ventilated alveoli, alveolar carbon dioxide pressure will coincide with arterial carbon dioxide pressure because of the almost rectilinear form of the carbon dioxide dissociation curve. On the contrary, because of the shape of the oxyhemoglobin dissociation curve, the blood that passes through the hyperventilated alveoli cannot increase much more its oxygen content and the oxygen pressure in the mixed arterial blood will remain lower than that of mixed alveolar air.

54. Kaltreider, N. L., and McCann, W. S.: Respiratory Response During Exercise in Pulmonary Fibrosis and Emphysema, J. Clin. Investigation **16**:23, 1937.

55. Krogh, M.: The Diffusion of Gases Through the Lungs of Man, J. Physiol. **49**:271, 1915.

C. Stratification of the Air in the Alveoli. Beitzke [56] has suggested an explanation on the basis of the imperfect mixing of gases within the alveoli. According to him, dilatation of the opening of the alveolar duct into the atrium will produce stratification of the gas, equilibrium being reached between the blood and the gas layer near to the alveolar wall but not between the blood and the more distant layers. Nevertheless, Christie [13] has analyzed this hypothesis and concluded that it cannot be maintained.

D. Arteriovenous Shunt. If blood is shunted through the lung without making contact with air (fibrotic or hepatized zones maintaining the circulation and the arterial changes) alveolar oxygen difference will increase markedly and alveolar carbon dioxide difference only slightly, as will be discussed in the second paper of this series.

It would be possible to differentiate the four conditions by giving the subject pure oxygen to breathe and comparing the oxygen pressure in alveolar air with that of arterial blood.

1. If alveolar oxygen difference is a diffusion gradient, oxygen breathing would diminish it and the value reached after the mixing in the lung is completed (about ten minutes) would be maintained during the period of oxygen administration. (For further discussion see Fasciolo and Chiodi.[57])

2. If caused by uneven ventilation, alveolar oxygen difference first would increase but later, when nitrogen has been washed out, would decrease.

3. If due to stratification of the gas within the alveoli, alveolar oxygen difference would increase, with no changes in time. Hyperventilation, however, is apt to reduce the increase.

4. If there exists an auriculoventricular shunt, alveolar oxygen difference would show a great increase, with no changes because of time or hyperventilation.

Although we did not investigate these points systematically, our results (see following paragraphs) do not support the view that an impairment of gas diffusion needs to be postulated as an explanation of the increased oxygen pressure found in these patients.

Effect of Breathing Pure Oxygen.—On Respiration: Table 10 shows the effect of breathing pure oxygen on the pulmonary ventilation in our group. In all cases, with the exception of case 10, the ventilation decreased while the patients were breathing oxygen, differences ranging from 100 to 1,390 cc. The respiratory frequency (table 11) either did

56. Beitzke, H.: Zur Mechanik des Gaswechsels beim Lungenemphysem, Deutsches Arch. f. klin. Med. **46**:91, 1925.

57. Fasciolo, J. C., and Chiodi, H.: Arterial Oxygen Pressure During Pure O_2 Breathing, Am. J. Physiol. **147**:54, 1946.

not change or was slightly decreased, with a tendency toward a decrease of the tidal air. Calculated as a percentage of the ventilation in air, the diminution (case 10 excepted) ranged from 6.34 to 26.5 per cent (table 10). The decrease of ventilation produced by oxygen has been observed by Ayerza, Solari and Berconsky,[14] Berconsky [17] and Capdehourat.[15] No significant correlation could be drawn between the depressor effect of oxygen and arterial carbon dioxide pressure, oxygen pressure, or the carbon dioxide effect on breathing.

TABLE 10.—*Effect of Oxygen and Carbon Dioxide on Ventilation in Patients with Pulmonary Disease* *

	Lung Ventilation, Liters per Minute							
Case	Breathing Air	Breathing Air Plus 4% CO_2	Breathing Pure Oxygen	Breathing Pure Oxygen Plus 4% CO_2	Effect of CO_2 in Air and in Oxygen, Liters per Minute	Ventilation While Breathing Oxygen and While Breathing Air, Liters per Minute	Increase by 4% CO_2 in Air, %	Ventilation While Breathing Oxygen and While Breathing Air, %
2	6.65	8.30	5.69	....	.....	—0.96	29.8	—14.4
3	8.37	12.51	7.05	12.90	—1.71	—1.32	49.5	—15.8
4	7.00	10.72	6.48	9.26	+0.94	—0.52	53.2	— 7.4
	6.96	11.11	5.78	8.41	+1.52	—1.18	60.0	—17.0
5	6.00	.....	4.41	....	.....	—1.59	....	—26.5
6	9.04	16.55	8.04	15.01	+0.54	—1.00	83.0	—11.1
7	7.72	14.46	7.23	13.21	+0.76	—0.49	87.4	— 6.3
8	6.48	9.62	6.38	7.02	+1.50	—0.10	48.5	— 1.5
	4.92	7.09	4.59	7.56	—0.80	—0.33	44.4	— 6.7
10	9.63	17.08	10.61	17.84	+0.22	+0.98	100.0 77.5	+10.2
13	7.54	11.28	6.54	9.61	+0.57	—1.00	51.5	—13.3
15	8.20	10.95	6.81	9.23	+0.33	—1.39	33.6	—16.6
	8.38	10.22	7.17	9.83	—0.82	—1.21	22.0	—14.4
17	5.34	6.75	4.79	6.34	—0.14	—0.55	26.4	—10.3

* Values are expressed in liters per minute at 37 C. and at the prevailing barometric pressure. The values of column 6, effect of CO_2 in air and in oxygen, were calculated by subtracting from the figures for ventilation during the breathing of 4 per cent carbon dioxide in air or in oxygen the values obtained when the subject was breathing air or oxygen respectively. In the last two columns the effects of carbon dioxide and oxygen on ventilation are expressed as percentages of the pulmonary ventilation when air was breathed.

On the Blood Oxygen Capacity: In 5 cases arterial blood was drawn before and during the seventeen to thirty minute period of oxygen breathing and its oxygen-combining capacity determined by the tonometric technic. It was decreased in 4 of the cases, ranging from 0.25 to 0.71 volume per cent. In 1 case an increase of 0.40 volume per cent was observed.

These results are in accord with those of Anthony,[58] who found a reduction of the hemoglobin and the red cell count in normal subjects breathing pure oxygen during fifteen to twenty minutes.

58. Anthony, A. J.: Der Einfluss kurzdauernder Sauerstoffatmung auf Hämoglobingehalt und Erythrocytenzahl des menschlichen Blutes, Ztschr. f. d. ges. exper. Med. **105**:417, 1939.

On Oxygen Pressure: The changes in the composition of arterial blood produced by breathing pure oxygen during seventeen to thirty minutes are summarized in table 12. The dissolved oxygen was calculated by subtracting from the total oxygen content of the arterial blood the oxygen-combining capacity as found by equilibrating a sample of the same blood in a tonometer, and from this figure arterial oxygen pressure was calculated with the use of the oxygen solubility coefficient. Although the values calculated by this method are too low (Fasciolo and Chiodi [57]), it is safe to compare the mean value in the Ayerza group with the one

TABLE 11.—*Effect of Oxygen and Carbon Dioxide on the Tidal Air and Respiratory Rate in Patients with Pulmonary Disease* *

	Tidal Air, Liters					Respiratory Rate, per Min.				
Case	Air	O_2	O_2—Air	4% CO_2	4% CO_2—Air	Air	O_2	O_2—Air	4% CO_2	4% CO_2—Air
2	0.37	0.38	+0.01	0.48	0.11	19	16	—3	18	—1
	0.39	0.35	—0.04	0.49	0.10	16	16	0	16	0
	0.40	0.37	—0.03	0.58	0.18	16	14	—2	14	—2
3	0.69	0.58	—0.11	0.89	0.20	12	12	0	14	+2
4	0.43	0.53	+0.10	0.76	0.33	16	12	—4	14	+2
	0.38	0.36	—0.02	0.61	0.23	18	16	—2	18	0
5	0.74	0.73	—0.01	....	....	8	6	—2	..	...
6	0.53	0.50	—0.03	0.82	0.29	17	16	—1	20	+3
7	0.59	0.60	+0.01	0.90	0.31	13	12	—1	16	+3
8	0.64	0.63	—0.01	0.80	0.16	10	10	0	12	+2
	0.41	0.38	—0.03	0.54	0.13	12	12	0	13	+1
10	0.50	0.64	+0.14	0.95	0.45	..	..	...	..	...
	0.58	0.64	+0.06	1.10	0.52	..	..	...	..	...
	0.80	0.96	+0.16	1.08	0.28	..	..	...	..	...
13	0.46	0.37	—0.09	....	....	..	..	...	..	...
	0.47	0.43	—0.04	....	....	18	18	0	..	...
15	0.29	0.27	—0.02	0.39	0.10	28	25	—3	28	0
	0.29	0.29	0.00	0.36	0.07	28	24	—4	28	0
17	0.26	0.23	—0.03	0.32	0.06	20	20	0	21	+1

* Volumes reduced at 37 C. and the prevailing barometric pressure.

obtained in a series of healthy persons. In 8 normal subjects the average value of arterial oxygen pressure was 543 ± 26 mm. of mercury, and in the patient group a mean value of 294 ± 40 mm. was obtained; the difference of 249 ± 48 is highly significant. This brought about a great increase of alveolar oxygen difference in the patient group, which, as pointed out before, must be considered evidence against the existence of generalized impairment in the diffusion of oxygen through the alveolar wall. Arterial carbon dioxide pressure rose in all the patients during oxygen breathing; this is due to the fact that the ventilation is depressed by the oxygen and therefore alveolar carbon dioxide pressure increases. In case 10, however, this explanation does not hold, as oxygen produced hyperventilation. It is possible that the arterial puncture had

produced pain and modification of the breath, causing carbon dioxide retention. Arterial p_H was found to be diminished in every case during oxygen breathing with the exception of case 10. This effect is due to two factors: (*a*) increased carbon dioxide tension and (*b*) increased oxygenation of arterial blood, with the corresponding changes of hemoglobin in the more acid oxyhemoglobin.

The effect of inhalation of oxygen on ventilation shows that in these patients the anoxemia stimulates respiration and that when the stimulus is withheld ventilation decreases. According to our present knowledge, the anoxic stimulation of breathing is produced through the carotid and aortic bodies. Therefore our results suggest that the chemoreceptor system is active in these patients.

TABLE 12.—*Changes Produced by the Breathing of Pure Oxygen in the Arterial Blood of Pulmonary Patients with Anoxemia*

	Ventilation, Liters per Minute			Arterial pCO_2, Mm. Hg			Arterial pO_2, Mm. Hg		Arterial p_H		
Case	Air	O_2	Difference*	Air	O_2	Difference	Air	O_2	Air	O_2	Difference
2.....	6.65	5.69	—0.96	64.8	73.0	+ 8.2	44.5	233	7.32	7.28	—0.04
4.....	7.04	6.32	—0.72	49.0	52.0	+ 3.0	53.0	516	7.36	7.34	—0.02
5.....	6.00	4.41	—1.59	59.5	71.0	+11.5	55.0	310	7.32	7.27	—0.05
7.....	7.72	7.23	—0.49	56.0	57.0	+ 1.0	49.0	326	7.33	7.32	—0.01
8.....	5.66	5.21	—0.45	62.0	72.0	+10.0	50.5	322	7.34	7.29	—0.05
10.....	9.1	10.34	+1.24	45.2	46.2	+ 1.0	43.5	229	7.33	7.33	0.00
13.....	7.32	6.19	—1.13	63.6	79.0	+15.4	44.5	162	7.32	7.24	—0.08
15.....	7.94	6.83	—1.11	67.2	78.2	+11.0	38.6	255	7.30	7.25	—0.05
Mean.....	....	....	—0.65	....	....	+ 7.6	....	...	....	....	—0.04

* The differences in the three columns were calculated by subtracting the values for air from the values for oxygen.

The effect of anoxemia on breathing could be explained in the following ways:

A. The anoxemia, acting through the carotid body, makes the respiratory center more sensitive to carbon dioxide and/or p_H. In this case carbon dioxide or p_H or both are still the respiratory stimulus, but the threshold has changed.

B. The low oxygen tension stimulates the respiratory center (via the carotid body) independently of carbon dioxide or p_H.

C. There should be a summation of the stimulus of the carbon dioxide and the oxygen on the respiratory center. The stimulus of both gases would be independent and proportional to their concentration in the blood.

In figure 1 the effect of breathing pure oxygen on the arterial blood of these patients has been represented. If "A" is admitted as the mech-

anism of the hypoxemic stimulation, the increase in the carbon dioxide pressure or the p_H decrease during the breathing of oxygen will be a measure of the degree of the potentiation of the respiratory center. If "*B*" or "*C*" is the mechanism, differences should be looked on as the increase in carbon dioxide or hydrogen concentration necessary to reach the threshold of the respiratory center and to regain the whole control of breathing.

Besides these changes, the heart rate slowed down during the oxygen inhalation, showing an average decrease of about seven beats per minute. This is in accord with the findings of Whitehorn and others [59] in normal subjects.

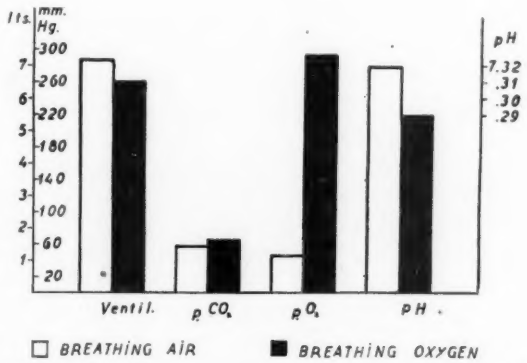

Fig. 1.—Effect of breathing pure oxygen on pulmonary ventilation, carbon dioxide pressure, oxygen pressure and p_H of the arterial blood in patients with pulmonary anoxia.

Effect of Carbon Dioxide on Breathing.—The effect of breathing 4 per cent carbon dioxide on ventilation, summarized in table 10, was an increase of 54 per cent over the ventilation as measured when the subjects were breathing air.

Shock and Soley [60] with a similar technic showed that the respiratory volume is doubled in healthy subjects breathing 4 per cent carbon dioxide in air. Our observations, as those of Scott [26] and Meakins and Davies [12] in patients with emphysema, show that for a given amount of carbon dioxide there is a smaller increase in the ventilation in these patients than in normal persons.

59. Whitehorn, W. V.; Edelmann, A., and Hitchcock, F. A.: The Cardiovascular Responses to the Breathing of One Hundred Per Cent Oxygen at Normal Barometric Pressure, Am. J. Physiol. **146**:61, 1946.

60. Shock, N. W., and Soley, M. H.: Effect of Oxygen Tension of Inspired Air on the Respiratory Response of Normal Subjects to Carbon Dioxide, Am. J. Physiol. **130**:777, 1940.

The increased ventilation is due to a deeper breathing, since respiratory rate showed only a small change. The heart rate was not significantly modified by carbon dioxide.

There is some correlation between the effect of carbon dioxide on ventilation and arterial carbon dioxide pressure, p_H and T40, which will be considered in the last paper of this series.

In order to decide if the anoxic stimulus potentiated the respiratory center to carbon dioxide, the effect of 4 per cent carbon dioxide in air (anoxic stimulus present) was compared with that of 4 per cent carbon dioxide in oxygen (anoxic stimulus withheld). In table 10, under column 6 are the results of subtracting the increase in ventilation from breathing 4 per cent carbon dioxide in oxygen from the increase produced by 4 per cent carbon dioxide in the air. If anoxemia had produced a potentiation of the respiratory center, the effect of carbon dioxide in air should be greater than that of carbon dioxide in oxygen.

TABLE 13—*Venous Pressure and Circulation Time*

Case	Venous Pressure, Mm. H_2O	"Decholin" Circulation Time, Seconds	Ether Circulation Time, Seconds
2	120	r.	10
3	134	22	8
4	135	18	9
6	100	28	10
8	95	20	14
9	65	26	..
10	95	..	18
11	180	..	10
12	210	..	..
13	130	29	15
14	270	23	11
15	310	32	20
17	120	19	11

Our results show that potentiation of the center was found to exist in 8 of 12 cases. In the remaining 4 the effect of carbon dioxide in air was less.

Although these findings do not permit us to draw conclusions, they suggest that at least in some cases anoxia can make the respiratory center more sensitive to carbon dioxide.

Circulation.—Venous Pressure (Table 13): Only 4 of 13 patients had elevated venous pressure (cases 11, 12, 14 and 15), and each of them had cardiac failure. The values in the remaining patients were within normal range whether or not they had cardiac insufficiency.

Weiss and Blumgart [61] found normal values in practically all their emphysematous patients. On the contrary, Kountz and Alexander [62] stated that the most constant circulatory finding in emphysema is an increased venous pressure. The discrepancies may be explained by differences in the measurement technics and the degree of emphysema and probably by the presence and the degree of cardiac failure.

Our results suggest that in pulmonary fibrosis and emphysema frankly elevated venous pressure is found only when cardiac insufficiency is superimposed. This is in agreement with the statements of Oppenheimer and Hitzig [63] and Kaltreider.[64]

Circulation Time (Table 13): "Decholin" circulation time was prolonged in most of the subjects. In 2 cases the values were below twenty seconds. Ether circulation time was increased in all the cases but 1, in which it was found to be in the upper normal range.

The increased circulation times with both methods were found in patients with the most severe degree of heart failure.

No evident correlation between venous pressure and circulation time was observed.

Different results are reported in the literature. Weiss and Blumgart,[61] working with radium C, found the arm to arm and pulmonary circulation times to be within normal limits in 21 of 25 emphysematous patients. As a matter of fact, some of these patients showed an increase in the velocity of the blood. Oppenheimer and Hitzig [63] found normal circulation times in patients with uncomplicated pulmonary emphysema, fast normal circulation times in some with a notable degree of cyanosis and polycythemia and prolonged circulation times only in the presence of frank myocardial failure. On the other hand, our results indicate that severe pulmonary emphysema and fibrosis with pronounced polycythemia result in prolonged circulation times even when there is no heart failure.

Blood Volume.—Determinations of blood volume were made on 10 patients who had Ayerza's syndrome with different degrees of anoxemia. Six of the patients had good circulatory function when determinations were made, the remaining 4 having failure of the right side of the heart.

The results obtained are found in table 14. Total blood volume ranged between 5.21 and 11.95 liters, which corresponds to 72.4 to 163.7 cc. per kilogram of body weight. These figures fall within

61. Weiss, S., and Blumgart, H. L.: Studies on the Velocity of Blood Flow: VIII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, J. Clin. Investigation **4**:555, 1927.

62. Kountz, W. B., and Alexander, H. L.: Emphysema, Medicine **13**:251, 1934.

63. Oppenheimer, B. S., and Hitzig, W. M.: The Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, Am. Heart J. **12**:257, 1936.

64. Kaltreider, N. L.: Differentiation Between Pulmonary and Cardiac Insufficiency in Chronic Pulmonary Disease, Internat. Clin. **4**:221, 1938.

TABLE 14.—*Blood Volume**

Case	Plasma Volume, Liters	Hematocrit, per Cent Red Cells	Red Cell Volume, Liters	Blood Volume, Liters	Blood Volume and Body Weight		Plasma Volume and Body Weight		Red Cell Volume and Body Weight		Blood Volume and Body Surface		O_2 Capacity, Volumes, per Cent	O_2 Saturation, per Cent	Venous Pressure, Mm. H_2O*	Circulation Time*	
					Cc./Kg.	Variation, per Cent	Cc./Kg.	Variation, %	Cc./Kg.	Variation, %	L./Sq. M.	Variation per Cent				Ether, Seconds	"Decholin," Seconds
2	2.28	60.2	2.93	5.21	74.8	— 1	32.7	—18	42.1	+ 24	3.30	+12.5	25.21	79.4	120	10	..
3	3.08	51	3.21	6.30	72.4	— 2	35.5	—12	36.9	+ 9	3.69	+26	24.84	87.5	124	8	22
4	2.14	71	5.25	7.39	112.0	+ 51	32.5	—19	79.5	+134	4.40	+50	30.0	87.4	135	9	18
6	2.82	52.7	3.15	5.97	82.9	+ 12	39.2	— 2	43.7	+ 29	3.58	+22	23.80	87.8	100	10	28
7	2.95	61	4.42	7.37	84.7	+ 14	33.9	—16	50.8	+ 50	4.10	+40	22.35	84.2	...	..	..
8	2.65	60	3.98	6.64	132.8	+ 79	53.1	+32	79.7	+135	4.23	+44	23.0	81.4	95	14	20
10	2.28	72	5.85	8.13	141.3	+ 91	39.6	— 1	101.7	+200	4.87	+66	27.87	77.3	95	18	..
13	2.50	70.1	5.84	8.34	146.4	+ 94	43.9	+ 9	102.5	+202	4.74	+61.5	26.23	71.0	110	19	31
14	3.00	67.9	6.35	9.35	112.6	+ 51	36.1	—10	76.5	+126	5.53	+89	.....	....	100	9	22
15	2.92	75.5	9.02	11.95	163.7	+121	40.1	0	123.6	+263	7.12	+142	27.3	68.6	160	19	23
Mean	2.66	64.1	5.00	7.66	112.4	+ 47.7	38.66	— 3.9	73.7	+115.4	4.56	+55.3	25.62	80.5	115.4	13	23

* Measured at the moment of the determination of blood volume.

our normal standard range (x) in 2 of the 10 cases and over it in the other 8. The increase in blood volume according to weight varied from 12 to 121 per cent. Since some of the patients had heart failure, with considerable edema, the blood volume in each patient was compared with our standard values according to meters of height. Accordingly, all the patients showed an increase in blood volume which ranged between 12.5 and 142 per cent, with a mean increase of 55.3 per cent in the whole group.

Plasma volume ranged between 2.28 and 3.08 liters, or 32.5 to 53.1 cc. per kilogram of body weight. In 3 patients the plasma volume per kilogram was within normal limits; in 5 there was a decrease which ranged between 10 and 19 per cent, and in 2 there was an increase of 9 and 32 per cent respectively. The average variation in the whole group was — 3.9 per cent.

Red cell volume varied from 2,935 to 9,025 cc., which gives a range between 36.9 and 123.6 cc. per kilogram. These figures are all above our normal mean standard values. The increase in the 10 cases varied from 9 to 234.1 per cent.

The results show that in Ayerza's syndrome there is an increase in the total blood volume which is mostly due to the increase in the red blood cells. Plasma volume did not change much in patients with chronic pulmonary disease. The deviation from normal of more than 10 per cent found for some patients according to weight can be explained by the fact that they were in cardiac failure with considerable edema, which leads to underestimation of the plasma volume per kilogram and/or undertreatment with mercurial diuretics. On the other hand, the only patient in whom plasma volume per kilogram was definitely increased was undernourished, and, as is known, this condition leads to overestimation of the plasma volume per kilogram.

Stimulation of the medulla by anoxemia appears to be the most important cause of the production of hypervolemia in Ayerza's disease. As has been previously mentioned, this anoxemia depends on hypoventilation of the lungs due to emphysema and fibrosis. Even though the higher blood volumes were obtained in patients with the higher degree of anoxemia, no good correlation could be found between arterial oxygen saturation and blood volume when ungrouped data were considered. On the other hand, when three groups of patients were distinguished according to the degree of arterial oxygen saturation, a definite correlation between these two factors was found (fig. 2).

Actually we are not able to explain the difference found in the reaction of patients with similar degrees of anoxemia. It is possible that some of these differences can be explained, as in case 4, on the basis that examination is performed shortly after a change in the arterial saturation has occurred and before the blood volume is given a chance to become equilibrated with it. However, we must admit also an individ-

ual response of the medulla to anoxemia, since even normal subjects react differently (Hurtado and others [44]). We are also unable to explain why some patients react to the anoxemia produced by the hypoventilation with an increase in the red cell volume and why others do not. This difference has also been pointed out by Kaltreider, Hurtado and Brooks.[43]

Since the higher values were obtained in patients with heart failure, the possibility exists that this condition may be the cause of a further increase in blood volume. Nevertheless, as these patients were also those in whom the lower values for oxygen saturation were found, we are unable to decide whether heart failure is a contributing factor or not.

Determination of blood volume in Ayerza's disease has been made previously in only 1 case by Lemon,[65] who also observed a decided

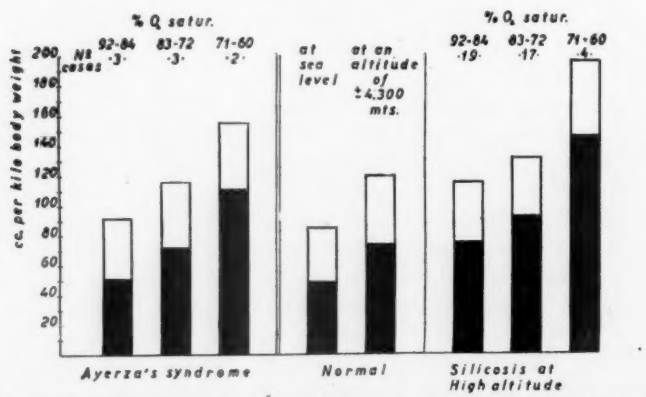

Fig. 2.—Data obtained on the mean values for the blood volume in the group with Ayerza's syndrome were compared with those obtained by Hurtado, Merino and Delgado [44] in normal persons at sea level and at high altitude and in persons with silicosis at high altitudes.

increase in the red cell volume. The changes in blood volume observed in these patients parallel those found by several workers in other types of anoxemia. Our results agree with those obtained in normal subjects at high altitude by Lippmann,[66] Lozoya Solis [67] and Hurtado and others.[44] They also agree with the results obtained by Hurtado [68] in

65. Lemon, W. S.: A Study of the Effect of Chronic Pulmonary Diseases on the Volume and Composition of the Blood, Ann. Int. Med. **3**:430, 1929.

66. Lippmann, A.: Blutzusammensetzung und Gesamtblutmenge bei Hochgebirgsbeiwohnern, Klin. Wchnschr. **5**:1406, 1926; cited by Hurtado and others.[44]

67. Lozoya Solis, J.: El volumen de plasma y de sangre circulantes en las altitudes y sus variaciones con la tiempo y con el ejercicio muscular, Arch. latino. am. cardiol. y hemat. **6**:241, 1936; cited by Hurtado and others.[44]

patients with Monge's disease and by Hurtado and his colleagues [44] in patients with silicosis at high altitude.

Cardiac Output (Table 15).—The well known difficulties in applying the rebreathing methods in subjects with gross alterations in the lungs, present in our patients, raise the question of whether the results are reliable or not.

Among all the cases, we chose for studying this function those in which the vital capacity and respiratory mechanisms seemed capable of allowing for the rebreathing technic.

The data in table 16 indicate the possibility of attaining a homogeneous mixture in the lung bag system before noticeable recirculation occurs. It shows the values of the arteriovenous oxygen difference

TABLE 15.—*Cardiac Output and Related Functions*

Case	Age	Body Surface,* Sq. M.	Heart Rate, per Min.	Oxygen Consumption, Cc./Min.	Arteriovenous Oxygen Difference, Cc./L.	Cardiac Output, L./Min.	Cardiac Index, L./Sq. M.	Systolic Output, Cc.	Systolic Output, Cc./Sq. M.
2	46	1.72	84	232	52.3	4.44	2.58	53	30.7
	..	....	87	223	50.5	4.41	2.56	51	29.5
3	53	1.99	67	254	69.0	3.68	1.85	55	27.6
	..	....	65	248	75.0	3.31	1.66	51	25.6
6	55	1.78	64	235	56.2	4.18	2.35	65	36.7
	..	....	60	233	61.9	3.76	2.11	63	35.4
	..	....	61	231	62.4	3.70	2.08	61	34.1
10	64	1.69	87	231	102.7	2.25	1.33	26	15.3
	..	....	87	225	109.9	2.05	1.21	23	13.9
	..	....	83	...	111.2	2.02	1.20	24	14.2
11	47	1.93	87	308	76.0	4.05	2.10	46	24.1
	..	....	94	308	64.0	4.78	2.45	50	26.1
12	65	1.85	64	217	74.2	2.92	1.58	45	24.7
	..	....	64	221	74.6	2.96	1.60	46	25.0
16	54	2.04	79	307	71.1	4.31	2.12	55	26.7
	..	....	78	311	70.9	4.39	2.15	56	27.6

* Edema free weight.

calculated between each pair of successive samples of the best determination on each subject. As can be seen, in every case it was possible to get at least two consecutive values for arteriovenous oxygen difference agreeing within highly satisfactory limits, the worst deviation being — 5.4 per cent from the mean in case 2.

Another test for the possibility of a good mixture in the lung bag system during rebreathing was elaborated, advantage being taken of the serial alveolar air experiments (table 17).

The subject in case 7 (R.A.) was chosen for this purpose because in the usual conditions there had been great differences in his successive samples of serial alveolar air. He was instructed to take a deep inspiration and then to expire gradually in a six second period as thoroughly

68. Hurtado, A.: Chronic Mountain Sickness, J. A. M. A. **120**:1278 (Dec. 19) 1942.

as he could. During this time four instantaneous samples were taken when the subject had expired 500, 1,000 1,500 and 2,000 cc. respectively (the last at the end of the six seconds). Several minutes later and after a deep expiration he had to rebreath from a bag containing 2,400 cc. of air, which simulated an ordinary cardiac output experiment. After twenty-two seconds of rebreathing, the three way cock was turned instantaneously at the end of a deep inspiration. The following deep expiration lasted six seconds and during it serial alveolar air samples were taken, as stated before. During these tests, moderate bronchial spasm was present.

TABLE 16.—*Detailed Results of Arteriovenous Oxygen Difference in the Most Reliable Test on Each Subject*

Case		2	3	6	10	11	12	16
Arteriovenous oxygen difference calculated between.....	Samples 1 and 2	81.0	**66.2***	**61.3**	**111.2**	82.6	74.6	57.0
	Samples 2 and 3	55.2	**69.0**	**64.6**	**106.6**	**76.0**	**73.8**	**68.8**
	Samples 3 and 4	**49.5**	**71.9**	**59.8**	**123.5**	**76.0**	117.6	**73.5**
Accepted arteriovenous oxygen difference....		52.3	69.0	61.9	109.9	76.0	74.2	71.1

* The figures in bold face were those considered valuable for the calculation of the accepted value.

TABLE 17.—*Serial Alveolar Air Before and Immediately After 22 Seconds of Rebreathing in Case 7*

Samples		I	II	III	IV
Before rebreathing.....	Volume of expired air in cc..	500	1,000	1,500	2,000
	CO_2, per cent.....	7.50	8.13	8.78	9.42
	O_2, per cent.....	13.04	11.75	10.00	8.23
Immediately after rebreathing	Volume of expired air in cc..	500	1,000	1,500	1,750
	CO_2, per cent.....	10.06	10.14	10.20	10.21
	O_2, per cent.....	9.16	8.74	8.21	7.88

The results in table 17 show that the maximal difference in carbon dioxide concentration in the four samples changed from 1.92 per cent in the first test to 0.15 per cent after the rebreathing. The behavior of the oxygen was satisfactory, the difference being 4.81 per cent before and 1.28 per cent after the rebreathing.

The mixture obtained in this case from deep rebreathing after a short period of rebreathing suggests that at least in some of the patients a homogeneous mixture could be obtained at the moment of the sampling in determinations of cardiac output. This in turn is in accordance with our data on arteriovenous oxygen difference discussed previously, and the two together give a strong support to the validity of the findings on cardiac output in our series.

In order to avoid changes in arterial saturation during the rebreathing period in cases in which there was low tension of alveolar oxygen,

mixtures were prepared to keep the average oxygen tension in the rebreathing samples as near as possible to that of the alveolar air. The difference between the two values for cardiac output in the subject in case 11 (table 15) may be ascribed to the fact that oxygen tension in the rebreathing samples was higher the first time and lower the second time than that of the alveolar air. The average may be considered as a better approximation to the true value for cardiac output.

Finally, even though the existence of a perfect equilibrium between alveoli and blood after the use of acetylene was not proved in our cases, we may accept it since Grollman and others,[69] using the acetylene method in patients with heart failure, pulmonary alterations and slight degree of arterial unsaturation, found alveolar-blood equilibrium in every case in which a homogeneous mixture in the lungs could be obtained.

In summary, it seems to us that determinations of cardiac output in our patients are reliable, but a direct unquestionable demonstration is lacking.

The subjects in cases 2, 16 and 6, who had never had cardiac insufficiency or signs of cardiac involvement, had a normal cardiac index (2.5, 2.1 and 2.2 respectively). The arteriovenous oxygen difference was normal in the first and third cases and higher than our normal limits in the second case (Suarez, Fasciolo and Taquini [70]).

The subject in case 11, who was under digitalis therapy because he had had cardiac failure, had a normal cardiac index. The patient in case 3, also with a history of heart failure, showed a diminished cardiac index.

The subjects in cases 12 and 10 were obviously in congestive failure. The former had a diminished cardiac index (1.6), with an arteriovenous oxygen difference in the highest normal range. The other had an extremely low cardiac index (1.2), with an increased arteriovenous oxygen difference.

The systolic output per square meter of body surface was diminished in all cases but 1 (case 6).

Our results indicate that in cases in which only respiratory insufficiency was present cardiac output was maintained at normal levels irrespective of the type of pulmonary alterations and the degree of arterial oxygen unsaturation and polycythemia. When cardiac insufficiency was added, cardiac output was diminished. This suggests a

69. Grollman, A.; Friedman, B.; Clark, G., and Harrison, T. R.: Studies in Congestive Heart Failure: XXIV. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, J. Clin. Investigation **12**:751, 1933.

70. Suarez, J. R. E.; Fasciolo, J. C., and Taquini, A. C.: Cardiac Output in Heart Failure, Am. Heart J. **32**:339, 1946.

direct correlation between functional capacity of the heart and cardiac output levels similar to that found in most of the cases of common heart disease (Suarez, Fasciolo and Taquini [70]).

Almost all the available data in the literature about patients with Ayerza's syndrome were secured with the indirect Fick method similar to that of Field, Bock and others.[71] In this way, Ayerza, Solari and Berconsky [14] and Arrillage, Berconsky and Taquini [15] obtained normal values. On the contrary, Cossio and Berconsky [72] and Capdehourat [18] found diminished cardiac outputs. These different results seem likely to be explained on the basis of the distinct cardiac involvement, as suggested by their protocols.

TABLE 18.—*Average Values of p_H and Oxygen and Carbon Dioxide Pressures of the Arterial and Venous Blood of Patients Suffering from Ayerza's Syndrome*

	Arterial Blood*			Mixed Venous Blood		
		Pulmonary Anoxemia with Increased Hemoglobin			Pulmonary Anoxemia with Increased Hemoglobin	
	Normal Persons	Not in Heart Failure	In Heart Failure	Normal Persons	Not in Heart Failure	In Heart Failure
pO_2, mm. Hg	95.00	48.7	47.7	35.00	31.7	28.0
pCO_2, mm. Hg	41.00	55.4	53.0	49.00	60.5	62.0
p_H	7.40	7.34	7.33	7.36	7.32	7.31

* Arterial values were obtained by direct analysis. Venous values were calculated from the arterial values and the arteriovenous difference.

A special consideration of Richards' data [73] is necessary. This author studied 6 cases of "cor pulmonale" with the method of catheterization of the right side of the heart and found normal cardiac outputs and arteriovenous oxygen differences. The paper gives only summarized data and does not allow for further consideration of the criteria used by the author for judging cardiac insufficiency.

COMMENT

Previous results showed that emphysematous patients have a decreased amount of tidal air and an uneven distribution of gases in the lungs. As a consequence, the efficiency of ventilation is decreased.

71. Field, H.; Bock, A. V.; Gildea, E. F., and Lathrop, F. L.: The Rate of the Circulation of the Blood in Normal Resting Individuals, J. Clin. Investigation **1**:65, 1924.

72. Cossio, P., and Berconsky, I.: Sindrome de hipoventilación alveolar: Estudio clínico y fisiopatológico de tres "cardíacos negros" (con una necropsia), Semana méd. **2**:917, 1932.

73. Richards, D. W., Jr.: Cardiac Output by the Catheterization Technique, in Various Clinical Conditions, Federation Proc. **4**:215, 1945.

In the early stage of the disease, full or partial compensation is achieved by increasing the respiratory minute volume, mostly as a result of auxiliary mechanisms of respiration. In the more advanced stages, when the diaphragm is lowered and the thorax is rigid, the ventilation of the lungs is not increased or decreased. As a consequence, the ventilation of the alveoli is impaired and carbon dioxide increases and oxygen decreases.

The low alveolar oxygen tension produces different degrees of anoxemia which stimulate the bone marrow and produce the hyperglobulia and the increase in hemoglobin present in the great majority of our patients. These changes keep the oxygen content of arterial blood around normal or slightly higher. On the other hand, the increase in the carbon dioxide tension leads to an increase in the $BHCO_3$ of plasma. Nevertheless, full compensation is not reached since p_H is slightly lower in these patients than in normal persons.

The changes in blood previously mentioned are important since they allow the patients to endure carbon dioxide and oxygen tensions that could not be endured by normal subjects.

Since these patients are able to increase their ventilation, either willingly or by breathing carbon dioxide, the question arises of why they have normal or only slightly increased ventilation, notwithstanding the low oxygen pressure, high carbon dioxide pressure and low p_H of their arterial blood. These paradoxic findings have been explained by the postulation of a depression of the respiratory center due to chronic anoxemia. However, chronic anoxemia does not seem to have a depressor effect on respiration since patients with cyanotic congenital heart diseases have increased pulmonary ventilation. It is possible to explain these findings without postulating a depression of the respiratory center by admitting that the abnormalities of the chest and lungs reduce ventilation although the nervous discharge of the neurons at the respiratory center is adequate for the composition of the blood at that moment.

Circulatory Changes.—Previous results show that in patients with Ayerza's syndrome without heart failure the cardiac output and the arteriovenous difference are normal. On account of the high viscosity of the blood the arterial pressure should increase, producing an overload of the anoxic cardiac muscle, for the maintenance of a normal cardiac output. Such a condition is avoided by increasing the blood volume and the vascular bed. These adaptations make the maintenance of normal cardiac output and a normal arteriovenous difference possible without a serious increase in peripheral resistance and with an extremely slow blood velocity, that is to say, without an increase in the cardiac work. In fact, the time employed by the blood to complete the circuit was calculated by dividing the blood volume by the cardiac output and

the average value found was nearly double the normal value as calculated in the same way. The slow blood velocity and the normal arteriovenous difference indicate that the blood flow per unit of time is normal. Such a result can be produced only by an increase of the capillary bed and of the total blood volume. It is interesting to note that although a normal oxygen content of arterial blood (volumes per cent) could have been obtained by merely decreasing the plasma volume, i.e., concentrating the cells to maintain a normal arteriovenous difference, blood velocity should increase.

The previously discussed mechanism nearly compensates the arterial changes produced by hypoventilation. As a result venous blood, which in turn can be accepted as a measure of the environmental condition of tissues, approaches normal, as table 18 shows. These results show that under basal conditions the tissues are maintained not far from normal. Moreover, since there is a great increase of the vascular bed and probably an opening of new capillaries, it is possible that distances from capillary to capillary are diminished. Then oxygen and carbon dioxide gradients should be smaller, and the conditions of cells could be further improved.

SUMMARY

In the group of pulmonary patients with mild to severe anoxemia pulmonary ventilation was found slightly increased; alveolar carbon dioxide tension was found to be higher and oxygen tension lower than in normal persons, indicating that alveolar ventilation was impaired. This alveolar hypoventilation in cases in which pulmonary ventilation was normal or even increased is produced by poor efficiency of ventilation. In our series the low efficiency was due to (*a*) uneven distribution of gases in the lung and (*b*) diminution of tidal air.

The main pulmonary disturbance of the group with Ayerza's disease was emphysema of the lung, as reflected by the figures of the total pulmonary capacity and its subdivisions. Vital capacity was found to be diminished, mainly because of a reduction of complemental air, reserve air being about normal. Residual air was increased, and total pulmonary capacity was slightly reduced. In some patients the basal metabolic rate was over the normal figures.

The oxygen dissociation curve of arterial blood at p_H 7.40 and 37 C. was not appreciably different from that of normal persons. At arterial p_H, owing to slight acidity of the blood, the curve was displaced to the right.

The oxygen capacity of blood was increased, keeping an inverse coarse correlation with the arterial oxygen pressure. The increase in hematocrit values was greater than that of hemoglobin, that is to say, the hemoglobin content per hundred cubic centimeters of cells was less than that in normal persons at sea level or at high altitude. The water content of red cells was increased in the 3 cases in which it was determined.

Arterial oxygen saturation and pressure were reduced below normal values in all the cases. The oxygen content of arterial blood of the group with Ayerza's disease was slightly elevated when compared with that in normal persons at sea level.

The alkaline reserve of plasma was increased, but that of the whole blood was normal on account of increased red cell volume. Values for carbon dioxide pressure and total carbon dioxide content of arterial blood were higher and for p_H lower than those in normal persons, which indicates a primary excess of carbon dioxide.

The alveolar-arterial oxygen difference was increased, and the evidence presented indicated that such an increase can be satisfactorily explained on the basis of unequal distribution of gases in the lung. Carbon dioxide pressure between alveoli and blood was not clearly increased.

That the arterial anoxemia was stimulating the breathing in these patients, probably through the carotid and aortic bodies, was shown by the depression of ventilation produced while they were breathing pure oxygen.

Breathing pure oxygen during seventeen to thirty minutes increased the arterial carbon dioxide pressure and decreased the p_H. The arterial oxygen rose to a pressure of about 300 mm. of mercury, less than that in normal persons under the same conditions. This finding is consistent with the hypothesis that the anoxemia is the result of an uneven ventilation of the alveoli.

The response to inhalation of carbon dioxide was less than that of normal persons. It was pointed out that this finding does not necessarily mean depression of the respiratory center.

In 8 of 12 cases the response to inhalation of carbon dioxide was greater when air was breathed than when oxygen was breathed, which suggests that in these cases the anoxemia had potentiated the respiratory center answer to carbon dioxide.

Venous pressure was higher than 150 mm. of water only in 4 cases of cardiac failure.

Ether and "decholin" circulation times were prolonged in almost every case.

The blood volume was increased, which was due primarily to an increase in red cell volume. The increase was roughly related to the degree of anoxemia. Changes in plasma volume were of minor importance.

Cardiac output was maintained at normal levels in cases uncomplicated by cardiac failure. When cardiac insufficiency was superimposed, diminished values were obtained.

The calculated oxygen pressures at the tissue levels in patients without cardiac failure was close to normal.

ACQUIRED ACUTE HEMOLYTIC ANEMIA OF UNKNOWN CAUSE

Report of a Case with Fibrinoid Arteritis, Atypical Pneumonia and Lower Nephron Nephrosis

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SAN FRANCISCO

THE RATHER scanty data on the lesions of acute hemolytic anemia have been reviewed recently by Damashek and Schwartz [1] and may be summarized briefly. Of 29 cases in which histologic changes in the spleen were described, hyperplasia of reticular or histiocytic cells with giant cell formation, erythrophagocytosis and myeloid metaplasia was prominent in 12; multiple infarction with thrombosis of veins and capillaries, in 6, and extreme hyperemia of the pulp, said to be similar to that in congenital hemolytic icterus, in 11. The spleens were enlarged from one and one-half to six times. Bone marrow was described as showing normoblastic hyperplasia in a few cases. Of the 10 necropsies in which the liver was examined hemosiderosis was noted in all but 1, which showed acute yellow atrophy. "Hemoglobinous infarcts" were described in a case in which a lethal reaction to transfusion had occurred.

The present case is reported partly because of the paucity of published data, but chiefly because of the fibrinoid vascular lesions, the lower nephron nephrosis and the unusual type of pneumonia.

REPORT OF CASE

History and Physical Examination.—The patient, a 20 year old white woman, of Italian descent, had been well all her life except for intermittent attacks of thrombophlebitis in the left leg. One month before her admission to Stanford Hospital she had had several "injections" for varicosities of the left leg. After the injections she lost her appetite and noticed increasing swelling of the left leg. Two weeks before her admission icteric scleras were observed, and she began to have attacks of nausea and vomiting with severe headaches and with pain in the chest. Three days before entry jaundice of the skin developed. She was hospitalized elsewhere for a condition diagnosed as acute leukemia and received four transfusions and penicillin. After two days, during which dyspnea, high fever and edema of the face developed, she was transferred to Stanford Hospital, on Dec. 21, 1947. On admission she was described as acutely ill,

From the Department of Pathology, Stanford University School of Medicine.

1. Damashek, W., and Schwarz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231 (May) 1940.

semicomatose and extremely dyspneic. Her face and left leg were edematous and her skin was jaundiced. There were signs of consolidation in the lower lobe of the right lung; the abdomen was distended, and liver and spleen appeared enlarged on percussion. There was generalized enlargement of the lymph nodes.

TABLE 1.—*Clinical Data in a Case of Acquired Acute Hemolytic Anemia*

Date	Urinary Volume, Cc./24 Hr.	Specific Gravity of Urine	Blood Urea, Mg./100 Cc.	Blood Pressure	Erythrocytes, Millions	Hemoglobin, Gm./100 Cc.	Transfusions, Cc.			Fluid Intake, Cc.	
							Plasma	Whole Blood	Red Cell Concentrate	Oral	Parenteral
12/21	875	1.011	60	.....	2.43	8.5	250	...	500	1,150	.....
12/22	1,820	.....	..	.....	2.56	10.3	500	...	.....	2,570	.....
12/23	2,000	.....	60	.....	1.77	7.04	...	...	.....	2,360	.....
12/24	1,880	.....	..	.....	0.97	4.52	...	...	1,000	2,500	.....
12/25	2,160	.....	..	.....	1.66	4.87	...	...	.....	2,510	.....
12/26	880+	1.012	..	.....	0.95	3.13	...	500	.....	920	.....
12/27	400+	1.011	..	.....	2.35	7.13	...	...	1,000	200	3,000
12/28	540+	.....	..	130/70	....	....	...	...	1.000	360	2,000
12/29	1,070	.....	..	146/90	....	....	...	...	1,000	845	2,000
12/30	670+	.....	..	.....	3.7	13.39	...	...	.....	520	2,000
12/31	1,520+	1.009	288	150/90	3.7	13.48	...	...	.....	1,530	800
1/1	1,740	.....	..	150/80	....	....	...	...	.....	1,640	.....
1/2	1,010+	1.008	324	.....	2.8	8.87	...	...	.....	630	2,000
1/3	2,250	1.010	318	.....	1.73	6.69	...	...	1,000	150	3,000
1/4	2,600	.....	..	118/70	2.27	7.13	...	...	500	100	3,000
1/5	2,350	.....	..	.....	2.2	8.78	...	...	500	15	2,000
1/6	3,000	.....	228	.....	....	....	...	...	.....	620	3,000
1/7	.....	.....	285	.....	2.3	8.0	500	...	.....	.....	.....

TABLE 2.—*Leukocyte Count in Case of Acute Hemolytic Anemia*

Date	Total White Cells	Differential White Cell Count, per Cent							
		Neutrophils		Eosinophils	Basophils	Lymphocytes	Monocytes	Myelocytes	Nucleated* Red Cells
		Banded	Segmented						
12/21	18,600	16	54	0	1	26	3	0	36
12/23	10,800	49	17	1	1	25	1	7	16
12/26	32,600	14	45	1	1	29	5	5	38
12/30	10,878	45	35	1	0	18	0	0	2
1/4	48,100	52	26	2	1	14	4	0	2
1/6	31,100	43	35	0	0	12	1	6	9
1/7	45,700	66	16	0	0	14	0	4	25

* Count per hundred leukocytes.

Laboratory Findings (tables 1 and 2).—Fragility of erythrocytes, tested on December 23, was within normal limits. Prothrombin time on December 27 was 49 per cent of normal. The platelet count was 160,000 per cubic millimeter on December 21 and 100,000 on December 27. On December 31 the mean corpuscular volume of the erythrocytes was 129 cubic microns, the mean corpuscular hemoglobin was 36 micromicrograms and the mean corpuscular hemoglobin concentration was 28 per cent. On several occasions the urine was cherry red, but no hemoglobin determinations were carried out on it. On December 21 there were about 5 granular casts and a rare erythrocyte per high power field in the centrifuged specimen. On December 31 and on January 2 and 6 no casts were observed in the urine. There were a few erythrocytes. No quantitative studies were carried out on formed elements in the urine. The patient's blood

was type O and she was Rh negative. Difficulty was experienced in obtaining compatible blood for transfusion, as the patient's serum contained atypical agglutinins with a wide range of action.

Course of Illness.—The patient was treated with multiple transfusions of red cell concentrate, plasma and whole blood (table 1). During the first four days her temperature remained about 39 C. (102.2 F.), but dropped on the fifth day, and her condition seemed improved. There was roentgenographic evidence at this time of some clearing of the pneumonia in the lower lobe of the right lung. Although her temperature remained lower for the next week, the improvement was only temporary. She became confused and disoriented. On the ninth day edema of the legs was noticed, and on the eleventh day the blood urea was 288 mg. per hundred cubic centimeters. Her temperature rose again on the

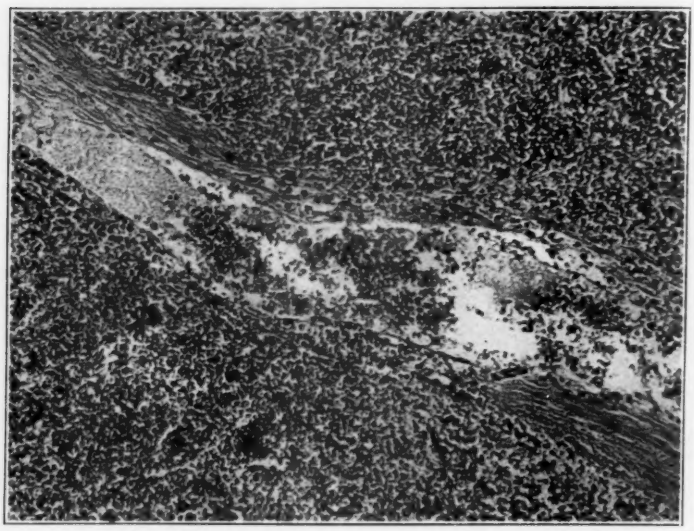

Fig. 1.—Spleen; × 150, hematoxylin and eosin stain. Infiltration and destruction of wall of trabecular vein.

thirteenth day, and she died rather suddenly on the eighteenth day after admission. The clinical diagnoses were: acute hemolytic anemia, pneumonia of the lower lobe of the right lung, acute nephritis and thrombophlebitis of the left iliac vein.

Autopsy (seven hours after death).—The skin and mucous membranes were intensely icteric. There was generalized subcutaneous edema. The diameter of the left leg was about one and one-half times that of the right. There were approximately 800 cc. of clear, yellowish green fluid in the left pleural cavity, 1,500 cc. in the right pleural cavity and 300 cc. in the peritoneal cavity. All the viscera were yellowish brown. The heart weighed 360 Gm. and was not remarkable except for an area of hyperemia, 2 cm. in greatest dimension, in the interventricular septum. The foramen ovale was closed. The left lung weighed 520 Gm.; the cut surface was edematous, and there were areas of con-

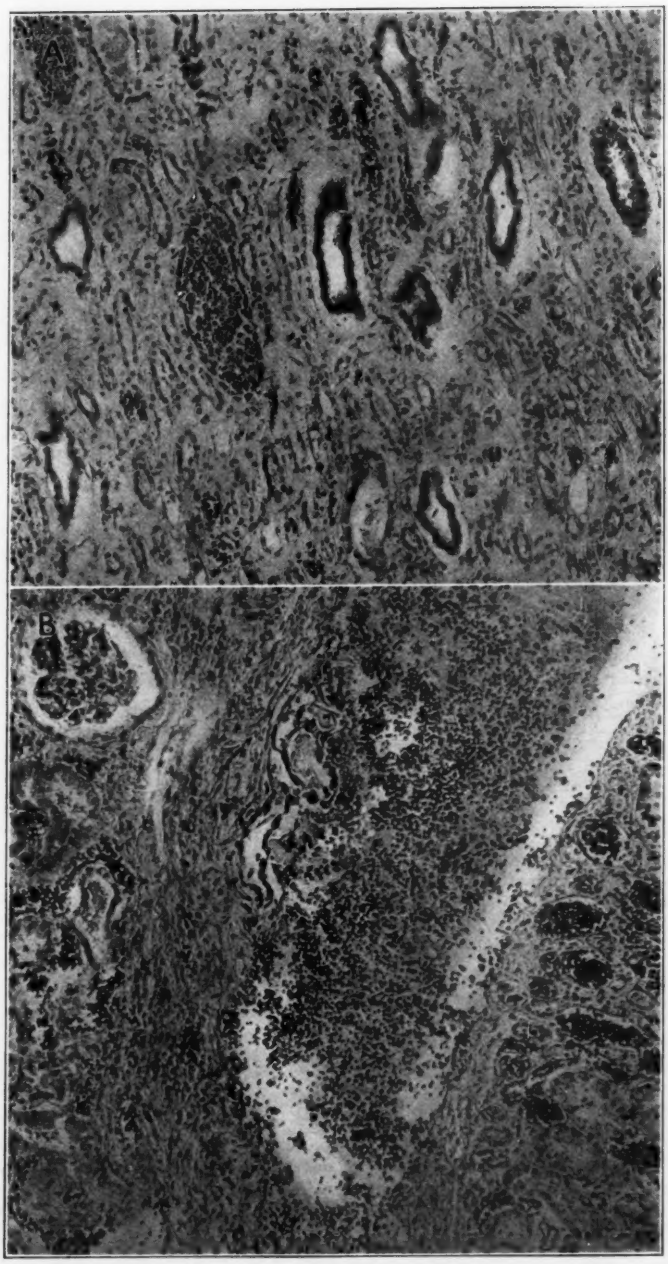

Fig. 2.—Kidney; × 150, hematoxylin and eosin stain. *A*, pigmented casts in collecting tubules; cellular infiltrate. *B*, rupture of necrotic tubule into vein: parietal thrombosis.

gestion but no consolidation. The right lung weighed 790 Gm., and on the external surface there were many intense purple blotches, which, on section, were observed to be granular and appeared to be small infarcts, although dissection of the pulmonary arteries revealed no thrombi. There was irregular consolidation of the lower lobe of the right lung. The liver weighed 2,700 Gm. and was bile stained. The lobular markings were visible. The spleen weighed 900 Gm., and, on section, there were noted many firm, yellowish gray areas of infarction, averaging 4 cm. in greatest dimension. The kidneys weighed 260 and 270 Gm. When dissected, they appeared somewhat bile stained but were otherwise not remarkable. The pelvic veins on the right were normal. The left iliac vein was completely thrombosed at a point 7 cm. from the bifurcation of the vena cava, with some extension up toward the vena cava.

Microscopic Examination.—Liver: The areas about the central veins of the liver were hyperemic, and the sinusoids everywhere were crowded with erythrocytes. Phagocytosis of erythrocytes by the Kupffer cells was definite and widespread. Many of the Kupffer cells contained masses of pigment, varying from light green to brown, most of the latter reacting to form prussian blue. The majority of the hepatic cord cells contained similar masses of pigment, some of which reacted to form prussian blue.

Spleen: The red pulp was packed with erythrocytes, reticular cells and plasma cells. There were many giant forms of reticular cells with huge, basketwork-like nuclei. These contained fragments of red cells. A large amount of intracellular pigment was present, much of which reacted to form prussian blue. The malpighian follicles were small, and the germinal centers were not active. There were fibrinoid alteration of the wall of a trabecular vein and infiltration of the wall by mononuclear cells (fig. 1). A few of the trabecular veins contained thrombus material. There were areas of recent infarction. Scattered throughout the pulp were collections of large cells with basophilic cytoplasm and large nuclei. Some of the cells had mitotic figures and suggested myeloid metaplasia.

Kidneys: In the cells of the proximal convoluted tubules, there were numerous small, brown granules which reacted to form prussian blue. These tubules were large and had the appearance of the hypertrophied nephrons observed in certain cases of chronic glomerulonephritis. In the boundary zone and pyramids were lesions characteristic of lower nephron nephrosis,[2] i. e., interstitial cellular infiltration, damaged collecting and distal tubules, pigmented casts within these tubules, (fig. 2*A*) and rupture of necrotic tubules into thin-walled veins (fig. 2*B*). In addition, there was evidence of myeloid metaplasia in the pyramids. This change took the form of clumps of basophilic cells, some in mitosis, lying within and adjacent to dilated capillaries in the medulla.

Vertebral Marrow: There was hyperplasia of all elements, particularly of the erythrocytic series. The erythrocytic hyperplasia was of the normoblastic type. No hemosiderin or other pigment was present.

Vascular Lesions: Those in the pancreas were best developed and will be described in detail. Figure 3*A* shows a pancreatic artery, with a diameter of about 300 microns. In the hematoxylin and eosin preparation, the collagen of the adventitia had a swollen, glassy, refractile appearance and was brightly eosinophilic. The muscular layer was interrupted at several points by a similar fibrinoid alteration. Surrounding the small artery was a scanty infiltration con-

2. Lucké, B.: Lower Nephron Nephrosis, Mil. Surgeon **99**:371 (Nov.) 1946.

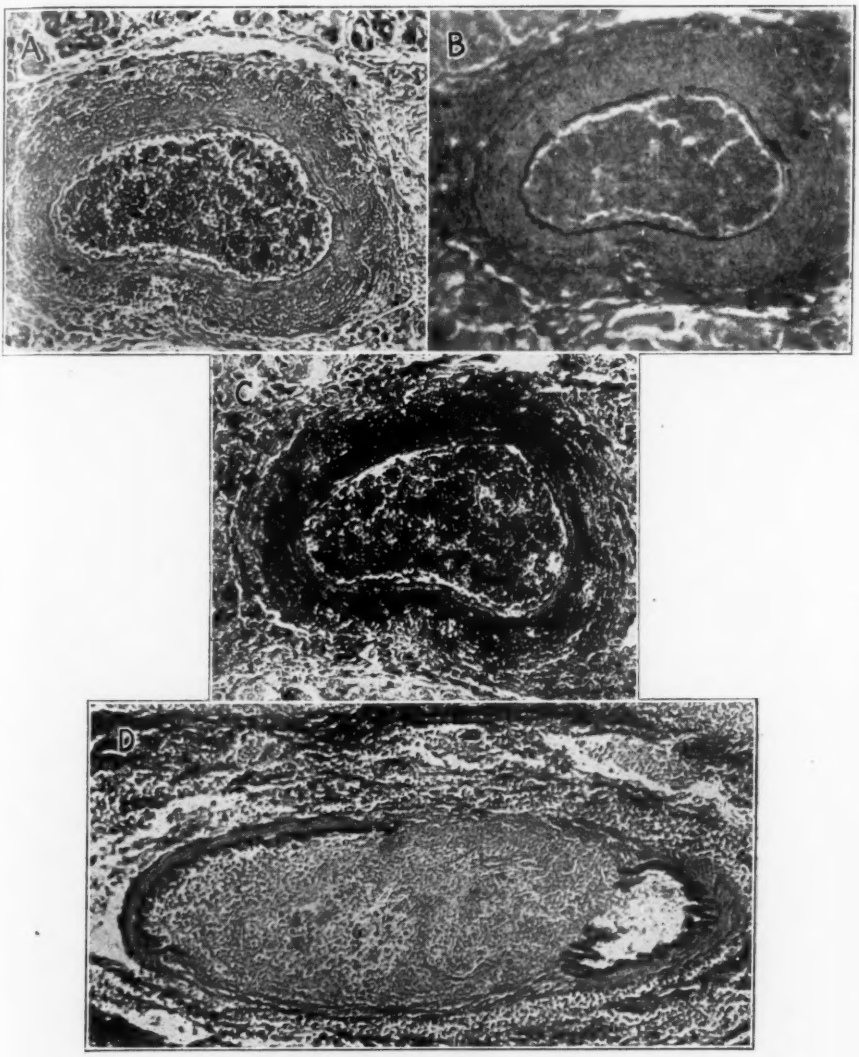

Fig. 3.—*A*, pancreatic artery, 300 microns diameter; × 150, hematoxylin and eosin stain. Thickened refractile collagen in adventitia. *B*, same artery, Van Gieson–Weigert stain, showing breaks in internal elastic membrane. *C*, same artery, azocarmine stain. The red-stained fibrinoid appears black. Involvement of entire thickness of the wall is shown. *D*, splenic artery, Van Gieson-Weigert stain, × 150. Destruction of internal elastic membrane and muscular wall.

sisting chiefly of large mononuclear cells with a few polymorphonuclear leukocytes and rare eosinophils. In the Van Gieson-Weigert preparation, the altered collagen and muscle stained yellow, whereas nearby normal collagen stained red, and at the

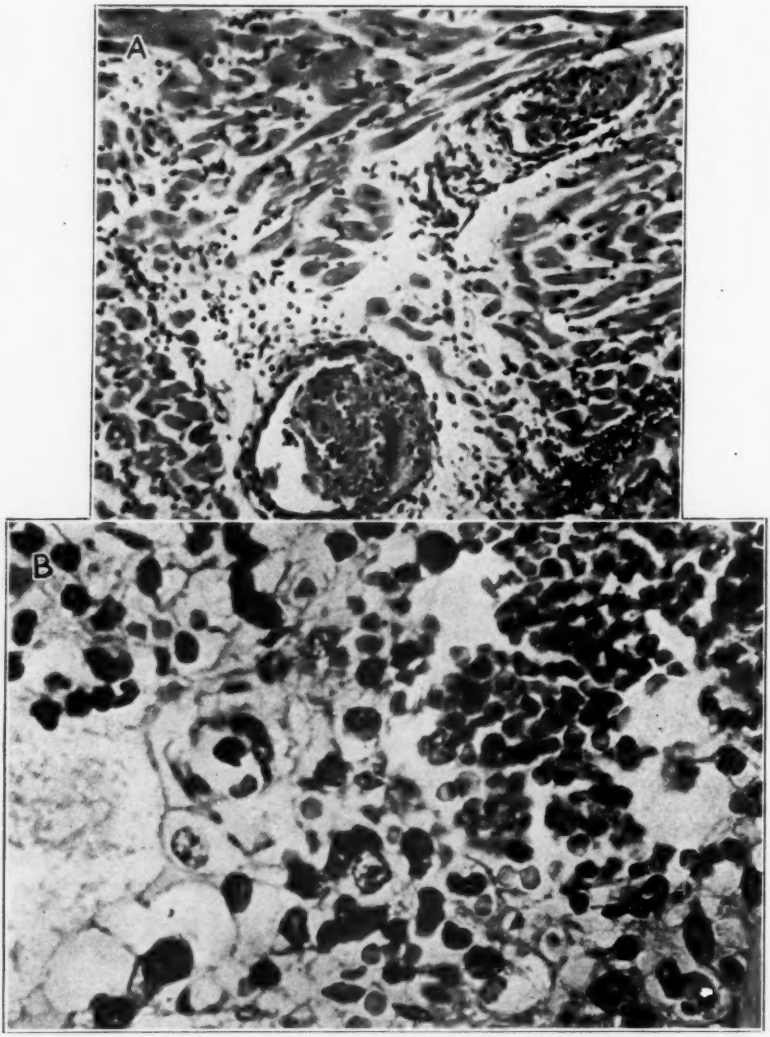

Fig. 4.—*A*, heart; × 150, hematoxylin and eosin stain. Thrombosis of small veins. *B*, right lung; × 450, hematoxylin and eosin stain. Atypical pneumonia in lower lobe.

points where the wall of the vessel was most involved the yellow material extended through to replace the internal elastic membrane, interrupting its continuity at

several points, as shown in figure 3*B*. In the azocarmine preparation (Heidenhain modification), the altered collagen and muscle of the vascular wall stained a brilliant red, appearing black in figure 3*C*, and the involvement of the entire thickness of the arterial wall at several points was clearly shown. In the phosphostungstic acid–hematoxylin stain, the fibrinoid substance appeared a deep purplish black, while normal collagen stained yellowish orange. Most of the arteries of comparable caliber in this section of the pancreas were involved. There was no thrombosis. An artery in the spleen, with a diameter of about 350 microns and lying in the center of an infarcted area, showed destructive thrombosing arteritis. In the Van Gieson-Weigert preparation (fig. 3*D*) the localized destruction of the muscular wall and internal elastic membrane was well shown. The infarct in the interventricular septum was estimated to be about twenty-four hours old. In the involved area there were many arterioles, with diameters of about 100 microns, which showed alterations in the internal elastic membrane and muscularis. Most of these vessels were thrombosed. There were thrombi in several small venules of the myocardium (fig. 4*A*). Similar thrombi were present in venules of the parathyroid glands.

Lungs: No vascular lesions of the sort observed in the pancreas were seen in the lungs, although there were organizing thrombi in some of the smaller vessels. One large vessel contained an unattached embolus, which appeared to have broken off from an organizing thrombus in the left iliac vein. Nearby was a small early infarct. Involving most of the lower lobe of the right lung was a pneumonia characterized by the presence of a peculiar interstitial infiltrate (fig. 4*B*). The infiltrating cells were plasma cells, lymphocytes and large mononuclear leukocytes. Some cells of the last type had very large nuclei and basophilic cytoplasm with tapered ends. Infiltration with polymorphonuclear leukocytes was relatively slight, and the bronchi were not primarily affected. Many of the alveoli contained fibrin, and there were fibrin plugs in the alveolar capillaries. There was widespread intra-alveolar hemorrhage. Megakaryocytes were numerous in the alveolar capillaries. No organisms were demonstrable in the bacterial stains. The anatomic diagnoses were: hemosiderotic pigmentation of the liver, spleen and kidney; ascites, hydrothorax and subcutaneous edema; edema of the lungs; chronic passive hyperemia of the liver and spleen; normoblastic hyperplasia of the bone marrow; thrombosis of the left external iliac vein with pulmonary embolism and multiple small infarctions; atypical pneumonia of the lower lobe of the right lung; lower nephron nephrosis; disseminated fibrinoid arteritis involving the pancreas, spleen and myocardium; recent infarction of the myocardium (interventricular septum) and spleen, and myeloid metaplasia of the spleen.

COMMENT

The cause of the acquired acute hemolytic anemia in this case was not determined. There was no morphologic abnormality of the erythrocytes, nor was their fragility increased. It is clear from the data in table 1, however, that transfused red cells were destroyed as fast as they were given. Very little hemoglobin was excreted in the urine, as far as can be judged from the available data. The data in table 1 also suggest that the volume of the urine was insufficient in relation to its low specific gravity. The persistent increase in blood urea was probably a consequence of the large amount of protein given intra-

venously despite renal insufficiency attributable to lower nephron nephrosis. Lucké [2] stated the belief that lower nephron nephrosis follows the destruction of large amounts of tissue or of blood; the latter condition was amply fulfilled in this case. It has been demonstrated that parenterally injected protein will maintain nitrogen balance in dogs,[3] and Addis [4] showed that in rats parenterally injected protein leads to great increase in urea in the urine. He pointed out that 1 liter of blood contains about 167 Gm. of protein (plasma protein plus hemoglobin), and stressed the potential danger in giving large amounts of blood in the presence of renal insufficiency.

Venous thrombosis has been described in cases of acute hemolytic anemia,[1] and in the case described here such thrombi were noted in small veins of the heart, parathyroid glands and spleen. The arterial lesions, however, were apparently unique. They were indistinguishable from those seen in cases of lupus disseminatus and periarteritis nodosa and were of the type stated by Rich and Gregory [5] to be indicative of hypersensitive reactions and by others [6] to be indicative of sharply rising hypertension. Table 1 shows only a mild, transient elevation of blood pressure in this case. The nature of the injections given one month prior to the patient's admission was not determined. In view of the time interval and the early development of the vascular lesions, the injections are unlikely to have been implicated in the pathogenesis. Sulfonamide compounds were not given at any time during the patient's stay at Stanford Hospital.

The atypical pneumonia closely resembled the type described by Rich [7] as characteristic of pneumonitis seen in rheumatic fever and in sensitization to sulfonamide drugs, and which he asserted to be of anaphylactic origin. No bacteriologic studies were carried out clinically. Morphologically, the process was not of the type seen in bronchopneumonia or lobar pneumonia, nor were organisms demonstrable in bacterial stains of the tissue. It is possible that the hemolysis,

3. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, Physiol. Rev. **20**:194 (April) 1940.

4. Addis, T.; Barrett, E.; Lew, W.; Poo, L. J., and Yuen, D. W.: Danger of Intravenous Injection of Protein Solutions After Sudden Loss of Renal Tissue, Arch. Int. Med. **77**:254 (March) 1946.

5. Rich, A. R., and Gregory, J. E.: Experimental Demonstration That Periarteritis Nodosa Is Manifestation of Hypersensitivity, Bull. Johns Hopkins Hosp. **72**:65 (Feb.) 1943.

6. Smith, C. C.; Zeek, P. M., and McGuire, J.: Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs, Am. J. Path. **20**:721 (July) 1944.

7. Rich, A. R., and Gregory, J. E.: On Anaphylactic Nature of Rheumatic Pneumonitis, Bull. Johns Hopkins Hosp. **73**:465 (Dec.) 1943.

the vascular lesions and the pneumonitis were all expressions of damage caused by a circulating antigen to which the patient was sensitized.

SUMMARY

A case of acquired acute hemolytic anemia of unknown cause is presented. The lesions, in particular disseminated fibrinoid arteritis, an atypical pneumonia and lower nephron nephrosis, are described and discussed.

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LUTEMBACHER'S SYNDROME

Report of a Case with Unusually Large Atrial Septal Defect

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IT IS somewhat paradoxic that often, even in persons of advanced years, the question of possible congenital cardiac disease enters prominently into the problems of differential diagnosis and prognosis. The commonest of all congenital defects, patent foramen ovale, frequently gives rise to no symptoms or signs throughout life and is discovered only at autopsy. Lutembacher's syndrome, a large atrial septal defect with concomitant mitral stenosis,[1] is an extremely uncommon combination of congenital lesions, which often does not become apparent until late in life, and the diagnosis of which is likely to be missed until autopsy. McGinn and White,[2] however, in 1933, pointed out that this combination of lesions may well be recognized before death if the possibilities of its occurrence and the distinctive roentgenographic findings are borne in mind, and Geiger and Anderson [3] have recently recorded a case in which the diagnosis was made ante mortem.

In the case of Lutembacher's syndrome recorded in this communication the atrial defect is believed to be the largest reported to date.

REPORT OF CASE

History.—G. E. R., a white man aged 31, was first seen on July 22, 1942, when the following history was obtained:

He had been considered a delicate, highly nervous child, though nothing in any way abnormal could be elicited concerning the neonatal period and infancy. A prominence of the left side of the chest had been noted in childhood but had apparently given rise to no symptoms. Nothing in his history suggested rheumatism or chorea. He completed elementary school and high school successfully and entered college, where, in 1932, he had some sort of acute febrile illness, which lasted only a few days. He was hospitalized for this period in the college infirmary, and then spent the next six months in bed at home and an additional six months in convalescence, apparently because continued weakness limited his activities. At some time during this illness tonsillectomy was performed.

From the Department of Internal Medicine, Vicksburg Clinic.

1. Lutembacher, R.: De la sténose mitrale avec communication interauriculaire, Arch. d. mal. du coeur **9**:237-260, 1916.

2. McGinn, S., and White, P. D.: Interauricular Septal Defect Associated with Mitral Stenosis, Am. Heart J. **9**:1-13 (Oct.) 1933.

3. Geiger, A. J., and Anderson, H. C.: Lutembacher's Syndrome Complicated by Acute Bacterial Endocarditis: Report of a Case Diagnosed During Life, Am. Heart J. **33**:240-249 (Feb.) 1947.

In 1933 the patient undertook sedentary work and had no further disability until 1936, when he had an illness which, he said, was diagnosed as pleurisy, though the diagnosis seemed questionable. This illness was of short duration and did not require cessation of activity. The patient then remained well until Feb. 28, 1942, when, while stepping down from a bus, he suddenly became weak and dyspneic and complained of palpitation. After hospitalization for fifteen days, he was able to return to work, but he continued to suffer from severe weakness, dyspnea and palpitation and could attend to his affairs only irregularly. In July 1942 he gave up work entirely. Shortly before he was examined at the Vicksburg Clinic, he had noticed swelling of the feet and enlargement of the abdomen, and he had again begun to suffer from dyspnea.

The patient was married and had two children, both of whom were living and well. His father had died at the age of 54 of a cerebral hemorrhage. His mother, three brothers and three sisters were living and well and were apparently normal in all respects.

Physical Examination.—Examination on July 22, 1942 showed a fairly well developed man of asthenic habitus, in a rather poor state of nutrition. He was extremely pale, and his skin was café au lait. Cyanosis was insignificant. Dyspnea was severe. The veins of the neck were only slightly engorged, and the arteries in the neck showed no abnormal pulsation. The precordial region of the left side of the chest was extremely prominent as compared with the right side. Expansion was poor on the left side. The breath sounds were bronchial in character in the base of the right lung posteriorly. There were no rales and no evidence of fluid on either side of the chest.

The heart was enormously enlarged. The apex impulse, which was diffuse, was located in the left midaxillary line, 16 cm. from the midline. The right border of dulness was 7 cm. from the midline. Auscultation showed an overactive heart, with grossly irregular rhythm and periods of bigeminy and trigeminy. The first heart sound, which was increased in intensity, was followed by a loud systolic murmur (grade 4 plus). The second heart sound was rather impure. There was a middiastolic rumble. The blood pressure was 125 systolic and 70 diastolic.

The liver also was enormously enlarged. There was no peripheral edema.

The urine showed occasional leukocytic casts, even more occasional granular and hyaline casts and 15 to 20 red blood cells per high power field. Other routine laboratory studies revealed nothing abnormal. The roentgenogram of the chest (fig. 1) revealed an enormous enlargement of both sides of the heart. The left border was prominent. There was relative absence of the aortic knob. The hilar shadows were prominent.

The electrocardiogram (fig. 2) revealed auricular fibrillation, right axis deviation, ventricular premature beats with trigeminy and an intraventricular conduction defect.

The clinical diagnosis, on the basis of the history, physical findings and laboratory data, was rheumatic heart disease with mitral stenosis and auricular fibrillation.

Course of Illness.—The patient was hospitalized from July 25 to Sept. 15, 1942. Treatment, which was directed toward relief of congestive cardiac failure, included restriction of fluids and administration of diuretic drugs and of digitalis in adequate dosage. The effect of a high potassium–low sodium diet was also tested. Under this regimen the patient improved considerably, but on several occasions he had sudden paroxysms of rapid heart action, the rate rising to a maximum of 180 beats per minute, though it remained regular. An electrocardiogram taken during one

of these episodes revealed ventricular complexes of supraventricular origin, with the impulses arising near the junctional tissues. These attacks were of short duration, and were readily relieved by morphine.

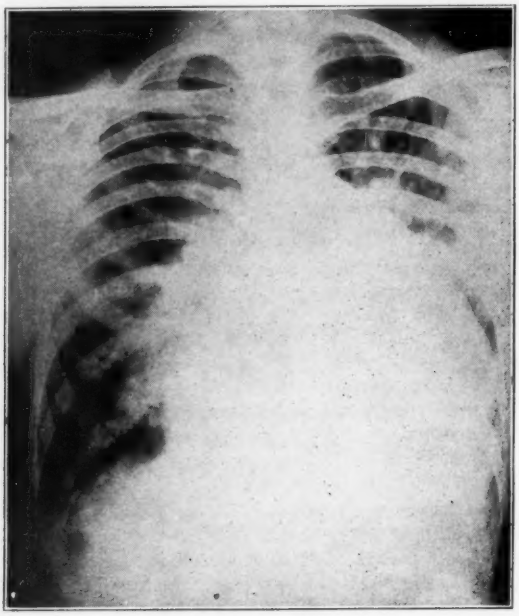

Fig. 1.—Roentgenogram of thorax (taken at 6 feet [180 cm.]), showing enormous enlargement of heart to both right and left, prominent left border, hypoplastic aortic knob, basal pulmonary congestion and prominent hilar shadows.

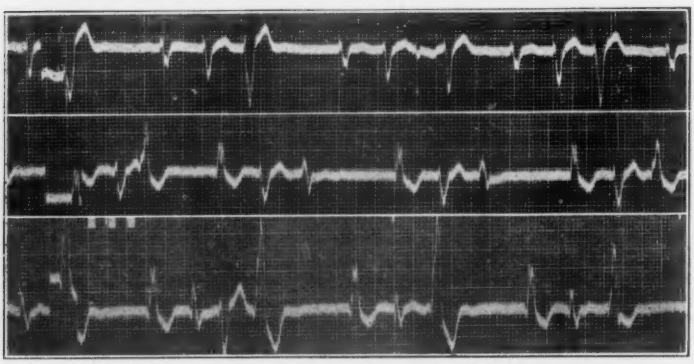

Fig. 2.—Electrocardiogram, showing auricular fibrillation, right axis deviation and intraventricular conduction defect.

After his discharge from the hospital on Sept. 15, 1942, the patient continued a bed and chair existence which constantly bordered on severe cardiac failure, in spite of the usual measures to prevent it. Frequent injections of mersalyl U.S.P. ("salyrgan") always produced effective diuresis and were not attended with unfavorable reactions.

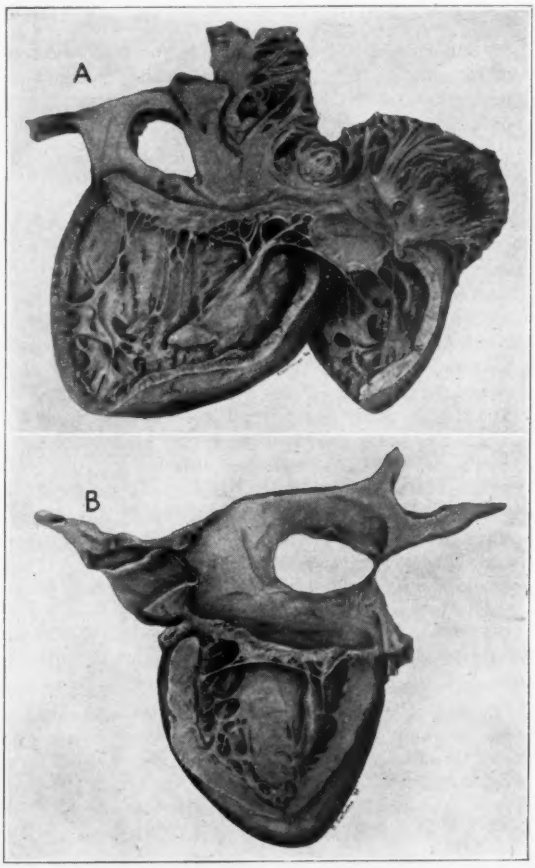

Fig. 3.—*A*, view of heart from right, after portions of huge right atrium were excised, showing large right ventricle and patent foramen ovale, with fimbriated margin, measuring 6 by 4 cm. *B*, view of heart from left, showing foramen ovale, roughened mitral valve and shortened chordae tendineae. Note disparity in size of the right and the left ventricle.

In July 1943 a pulmonary infarction developed, with severe pain in the chest and expectoration of bloody sputum. Thereafter the course of the illness was without special incident until Jan. 1, 1944, when the usual signs of congestive cardiac failure again became pronounced. An ampul of mersalyl was given intravenously, without immediate reaction, and about an hour after it had been

administered the patient's wife left his room. When she returned shortly afterward, he was dead. The exact mechanism of death could not be determined; but, since the patient died soon after the injection of mersalyl, death was perhaps the result of ventricular fibrillation, which is the apparent cause of the occasional sudden deaths following the use of this drug.

Necropsy.—The essential portions of the report of the necropsy, performed by Dr. J. C. Henthorne, are as follows:

The body was thin and well developed. The left side of the chest was somewhat more prominent than the right. The peritoneal cavity contained no free fluid. There was approximately 500 cc. of serous fluid in each pleural cavity. Fibrous adhesions were seen at the base of the right lung. The pericardial cavity contained about 1,000 cc. of serous fluid.

The transverse diameter of the pericardial sac was 23 cm., the most striking feature of the enlargement being the size of the right atrium, which alone was about the size of a normal heart. The atrium measured 13 cm. in transverse diameter, from the medial wall to the tip of the auricular appendix. It collapsed as soon as the heart was removed.

When the heart was opened, it was observed that hypertrophy of the right atrium and the right ventricle chiefly accounted for the cardiac hypertrophy. The right ventricle measured 11.5 by 9.5 by 3 cm. The wall was 0.7 cm. thick. The collapsed right atrium, when it was opened, measured 10.5 by 10 by 11 cm. The columnae carnae and the papillary muscles were hypertrophied. The coronary sinus was dilated. The foramen ovale was patent (fig. 3) and measured 6 by 4 cm. A remnant of fibrous membrane was attached to its border. Numerous thrombi were attached to the endocardium of the right auricular appendix.

The heart weighed 810 Gm. The aortic valve measured 6.6 cm. and the mitral valve 10 cm. The free border of the mitral valve was thickened, and the chordae tendineae, attached to the posterior cusps, were thickened and shortened. The tricuspid valve measured 15.5 cm. and the pulmonary valve 10 cm. The cavity of the left ventricle measured 10 by 6 by 4 cm.; the wall was 1.2 cm. thick. All valves except the mitral valve were normal in appearance, and the myocardium appeared normal.

There was slight atheromatous sclerosis of the coronary arteries. The pulmonary artery, which was greatly dilated, measured 4.5 cm. in diameter.

The liver weighed 2,000 Gm. It was moderately congested, and its edge lay 7 cm. below the costal margin. Careful examination of the spleen, kidneys, pancreas, adrenal glands, gastrointestinal tract, urinary bladder and prostate revealed no abnormalities.

COMMENT

The combination of abnormalities known as Lutembacher's syndrome was first recorded by Martineau in 1865 but was not fully described until Lutembacher's contribution, in 1916.

As already stated, small openings in the atrial septum, in the form of patent foramen ovale (patent ostium secundum), are the most frequent of all congenital cardiac defects. Defects larger than 1 cm. in diameter, however, are not at all common. Roesler,[4] in a complete review of the literature on the subject from 1826 to 1933, noted only

4. Roesler, H.: Interatrial Septal Defect, Arch. Int. Med. **54**:339-380 (Sept.) 1934.

61 such cases, to which he added a case of his own. In 30 of the 62 cases there was also a definite lesion of the mitral valve, and in 11 other cases a similar lesion was suspected. Not all the reports of the combined lesions included in Roesler's collection seem to be authoritative. McGinn and White,[2] in a critical review of the literature up to 1933, found only 23 instances of large atrial septal defect accompanied with mitral stenosis, and autopsy figures suggest that the smaller number is more likely to be correct: Traum [5] found only a single instance of Lutembacher's syndrome listed in 700 necropsy reports filed in the Veterans' Hospital Cardiac Research Unit, and only 2 instances were identified in 6,800 postmortem examinations at the Massachusetts General Hospital.[2]

Large atrial septal defects have been observed almost exclusively in women. In the 23 cases collected from the literature by McGinn and White,[2] only 1 of the patients was a man; their own patient, like the patient in the case recorded in this communication, was a man.

Pathogenesis.—Atrial septal defects are the result of failure of development and fusion of three structures: (1) the endocardial cushions, (2) the septum primum and (3) the septum secundum.[6] In the normal course of embryonic development, a primary septum grows downward from the superior and posterior portions of the (then) single atrial cavity to meet the endocardial cushions, which develop from the inferior portion of the (then) single atrium. The fusion of these two structures obliterates the ostium primum, the primary communication between the two atria. If there is failure of fusion, the result is the defect known as persistent ostium primum. Later an opening, the foramen ovale, or ostium secundum, is formed in the primary septum, and still later a septum secundum is formed to the right of the foramen ovale. In the normal course of development, the foramen ovale is closed by the fusion of these two septums at birth, or soon afterward. If there is failure of fusion, the result is the defect known as persistent ostium secundum, or patent foramen ovale.

There are at least three theories of the relation of the atrial septal defect to mitral stenosis in Lutembacher's syndrome. Lutembacher [1] himself stated the belief that the mitral stenosis was congenital and was the primary defect, his theory being that the increase of pressure, caused by the stenosis, within the left atrium prevents closure of the septum. Von Rokitansky [7] advanced the theory that hypoplasia of the aorta, which is usually present in this syndrome, is the primary cause of septal failure.

5. Traum, A. H.: Interauricular Septal Defect with Mitral Stenosis—Lutembacher's Syndrome, M. Bull. Vet. Admin. **20**:274-276 (Jan.) 1944.

6. Tinney, W. S., and Barnes, A. S.: Interauricular Septal Defects, Minnesota Med. **25**:637-643 (Aug.) 1942.

7. Von Rokitansky, cited by Roesler.[4]

His reasoning was that when hypoplasia of the aorta is present increased pressure in the left side of the heart prevents closure of the atrial septum. The fallacy in this reasoning is that such defects of the atrial septum do not occur in congenital aortic stenosis or atresia.

Most authorities accept neither Lutembacher's nor von Rokitansky's theory but regard the mitral stenosis as an acquired rheumatic lesion.[8] This theory is supported by the fact that in a quarter of the cases of large atrial septal defects on record no accompanying mitral stenosis was noted. It is probable that in this, as in other cardiac lesions, minor congenital defects in the mitral valve make it more susceptible to a rheumatic process. The frequent occurrence of auricular fibrillation in cases of Lutembacher's syndrome favors the concept of an acquired rheumatic lesion of the mitral valve, though against the theory is the fact that a positive history of rheumatic infection was obtained in only 3 of the 24 cases collected by McGinn and White,[2] including their own. It was present in the case reported by Geiger and Anderson,[3] but not in the case reported in this communication.

Anatomic Lesion.—Large atrial septal defects are usually single, though not infrequently the margins show fenestration. The defect is usually oval, and the diameter in the cases recorded to date has varied from 1.0 to 5.5 cm.[4] The heart is usually globular, and the enlargement is often enormous. It is chiefly the result of hypertrophy of the right auricle and the right ventricle, both of which are likely to be tremendously dilated. Recorded cardiac weights have varied from 250 to 1,035 Gm.[4] The pulmonary artery is greatly dilated, and the aorta is usually hypoplastic. The accompanying defect of the mitral valve may vary from slight roughening of the cusps to such extreme stenosis that only a minute orifice remains. In the case recorded here, the patent foramen ovale measured 6 by 4 cm., the defect being apparently larger than any previously observed.

Clinical Picture.—The presenting symptoms and signs in Lutembacher's syndrome are usually breathlessness, peripheral edema, palpitation and cough. In other words, the clinical picture is suggestive of congestive cardiac failure. Patients afflicted with this anomaly are usually described as being of delicate or of asthenic habitus. They frequently present a prominent deformity of the precordium, with bulging on the left. Cyanosis is uncommon except as a terminal event, when the admixture of venous with arterial blood reaches 33 per cent. Clubbing of the fingers is also uncommon. The clinical observations in the case recorded here were generally those described.

The cardiac rhythm may be normal, though premature beats are common, and auricular fibrillation, as in this case, is likely to occur at

8. McGinn and White.[2] Roesler.[4]

some time in the course of the disease. The presystolic murmur typical of mitral stenosis is the predominant finding in most cases, though sometimes no murmurs at all, or only a systolic murmur, can be detected. In patients with fibrillation, as in this instance, the middiastolic rumble of mitral stenosis may be heard. It must be remembered, however, that such a rumble may be heard, even when mitral stenosis is absent, as the result of the passage of blood through the hardened, calcified or fenestrated margins of the patent foramen ovale. When an apical thrill is present, which is frequent, it corresponds in time with the more prominent murmur present. The blood pressure is usually within normal range. Paroxysmal ventricular tachycardia, as in this case, is relatively common and no doubt bears a causal relation to the sudden death often observed in this condition. Subacute bacterial endocarditis, although common with other congenital cardiac lesions, is unusual with Lutembacher's syndrome.[9]

Roentgenographic and Electrocardiographic Findings.—The majority of writers agree that the diagnosis of Lutembacher's syndrome, though it may be suspected on the basis of clinical manifestations,[10] is almost never justified without roentgenographic confirmation. The roentgenogram of the thorax is characteristic.[11] The heart appears globular and is likely to be enormously enlarged in all directions (fig. 1). Roesler [4] stated that four other factors are necessary for diagnosis: (1) an enlarged pulmonary conus, (2) extensive hypertrophy of the right side, (3) wide hilar shadows and (4) a diminished aortic knob. Fluoroscopic examination confirms the roentgenographic findings and may occasionally reveal calcification in the mitral valve or in the annulus fibrosus.

The large shadows in the hilus (fig. 1), which Roesler [4] regarded as necessary for a diagnosis of Lutembacher's syndrome, have occasionally been mistaken for lymph nodes, and even for tumors. Two patients, in fact, were subjected to exploratory operation for a possible pulmonary neoplasm.[11c]

As in cases of most other congenital cardiac defects, there is nothing pathognomonic about the electrocardiographic findings in cases of Lutembacher's syndrome. In view of the presence of two anatomic

9. McGinn and White.[2] Geiger and Anderson.[3] Tinney and Barnes.[6]

10. (*a*) McGinn and White.[2] (*b*) Bedford, D. E.; Papp, C., and Parkinson, J.: Atrial Septal Defect, Brit. Heart J. **3**:37-68 (Jan.) 1941.

11. (*a*) McGinn and White.[2] (*b*) Tinney and Barnes.[6] (*c*) Baylin, G. J.: Patent Interauricular Septum Associated with Mitral Stenosis: Lutembacher's Syndrome, Radiology **38**:1-6 (Jan.) 1942. (*d*) Masters, A. M.: The Electrocardiogram and X-Ray Configuration of the Heart, ed. 2, Philadelphia, Lea & Febiger, 1942.

defects which cause enlargement of the right side of the heart, one might expect to find greater right axis deviation than would be present with atrial septal defects alone. This is not always true. Right axis deviation is common,[12] but is also frequently absent. It was present in only 1 of the 9 cases of large atrial septal defects reported by Schnitker.[13] While its presence may be a confirmatory sign of Lutembacher's syndrome, its absence does not exclude the diagnosis.

Because of the great hypertrophy and dilatation of the right atrium, the large P waves frequently seen in leads I and II in cases of Lutembacher's syndrome are not unexpected. The waves are frequently notched and bear no direct relation to the degree of atrial enlargement. Abnormal forms of the QRS complex are common, as are biphasic QRS complexes of the type often associated with extreme hypertension. Intraventricular conduction defects are common. There are no significant changes in the T waves.

Auricular fibrillation is frequent with Lutembacher's syndrome,[6] although it is not usually encountered in other types of congenital cardiac disease. It is also seldom seen in patients under 50 years of age having atrial septal defects without concomitant mitral stenosis. The extreme dilatation of the auricles is an important factor in the causation of the disturbed rhythm.

Prognosis.—Patients with Lutembacher's syndrome are often capable of a surprising amount of physical exertion. Firket's [14] patient passed successfully through eleven pregnancies and three abortions and lived to the age of 74 years. One of Lutembacher's own patients was 61 years of age and had had seven pregnancies without evidence of cardiac failure. Bonnabel's [15] 2 patients were 62 and 74 years of age, respectively. Erickson and Willius,[16] who stated that the average duration of life in patients with large atrial septal defect is only 32.5 years, themselves reported a case in which the patient lived to be 68 years old.

Lutembacher's syndrome is therefore not incompatible with a relatively long span of life. On the other hand, the prognosis in these cases is uncertain, and death is likely to occur, usually rather suddenly, at or near 35 years of age, as in the case recorded in this communication.

12. Roesler, H.[4] Bedford, Papp and Parkinson.[10b]

13. Schnitker, M. A.: The Electrocardiogram in Congenital Cardiac Disease, Cambridge, Mass., Harvard University Press, 1940.

14. Firket, cited by White.[17]

15. Bonnabel, J.: Contribution à l'étude de quelques affections congénitales du coeur compatibles avec l'existence et de leur pronostic, Thesis, Paris, 1906, no. 39.

16. Erickson, C. W., and Willius, F. A.: Cardiac Clinics: Cardiopathy of Undetermined Origin: Enormous Cardiac Enlargement, Recurrent Congestive Failure, Heart Block, and Cerebral Embolism; Clinical and Postmortem Findings, Proc. Staff Meet., Mayo Clin. **11**:248-253 (April 15) 1936.

One possible explanation for the prolongation of life is that the septal defect somewhat relieves the burden imposed on the pulmonary circulation and on the right side of the heart by the presence of mitral stenosis.[17]

SUMMARY

The case of Lutembacher's syndrome (large atrial septal defect with concomitant mitral stenosis) described in this communication has been put on record because the septal defect is apparently the largest yet to be reported. The diagnosis in this case was not made ante mortem, although in retrospect it is evident that the patient presented all the important phenomena characteristic of this condition.

Vicksburg Clinic.

17. White, P. D.: Heart Disease, ed. 2, New York, The Macmillan Company, 1937.

RENAL INSUFFICIENCY DUE TO PAROXYSMAL COLD HEMOGLOBINURIA

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AND
HERBERT J. KAYDEN, M.D.
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PAROXYSMAL cold hemoglobinuria due to destruction of red cells has been regarded as a troublesome though nonfatal result of syphilis. Its rarity is reflected in the report of Thurmon and Blain, who noted its occurrence in 1 of 17,300 patients admitted to the Massachusetts General Hospital.[1] While late congenital syphilis claims the larger number of victims, acquired syphilis in the tertiary stage accounts for a noteworthy fraction of the cases.

The clinical syndrome may be suspected when malaise, myalgia, headache and abdominal cramps are climaxed by a severe shaking chill reminiscent of a malarial rigor occurring from several minutes to hours after exposure to cold. Fever usually follows these events and lasts for an hour or two. When intravascular hemolysis is sufficiently severe, free hemoglobin traverses the glomerular filter and appears in the urine for a variable length of time depending on the severity of the hemolytic episode. Persisting abdominal cramps or Raynaud's phenomena are a token of the extensive vasoconstriction which takes place. Sometimes urticaria plays a dominant part in the symptomatology. The patients are depleted and often anemic after a hemolytic attack.

Since it is the rule for patients to recover from such episodes and remain in a state of health reflecting only the other accompaniments of late syphilis, a case in which renal insufficiency terminated fatally should be of interest because of its rarity. In addition, some of the problems posed by this report may have a bearing on the course and prognosis of kindred ailments, such as the necrotizing renal processes following mismatched transfusion and crush injury.

Associate attending physician (Dr. Sussman) and assistant, Cardiovascular Research Unit (Dr. Kayden), Medical Service of Beth Israel Hospital.

1. Thurmon, F., and Blain, D.: Paroxysmal Hemoglobinuria; Observations Based upon Study of Three Cases, Am. J. Syph. **15**:350-367, 1931. Mackenzie, G. H.: Paroxysmal Hemoglobinuria, Medicine **8**:159-191, 1929.

REPORT OF A CASE

W. E., a 56 year old married Negro porter, entered the hospital on Jan. 14, 1944, because of passage of "reddish urine" five days before. He reported having had eleven similar episodes in the past two years with a similar clinical pattern.

After exposure to cold weather, the patient was seized with a severe shaking chill accompanied by pain in the lower part of the back and the legs, followed by a desire to urinate. This usually resulted in the passage of bright or dark red urine, followed by fever and ringing in the ears. These symptoms ordinarily lasted half a day or less. After each attack the urine returned to a normal color and the patient was undisturbed until the succeeding attack. Spring and summer seizures never occurred.

The last episode occurred on Jan. 9, 1944, after prolonged exposure to cold. This attack was extraordinarily severe and lasted a longer time than previous seizures. Pain in the lumbar region was prominent from the onset to the time of the patient's admission to the hospital.

Despite an adequate fluid intake, the urinary output had been meager, though the red color had disappeared since the day of the attack. For four days before his entrance to the hospital, and for the first time in his life, the patient was distressed because of shortness of breath. Several small hemoptyses accompanying a cough had also occurred two days before admission.

His past history disclosed a gonorrheal infection in 1918 and a chancre, apparently syphilitic, in August of 1937. Antisyphilitic treatment was administered for two and a half years (October 1937 to March 1940) so that a total of twenty-eight arsphenamine, twenty mercury and eighteen bismuth injections was given. During October of 1938, the Wassermann reaction was reported as 4 plus. In March 1939 the reaction to the Kline test was 3 plus, and in February 1940 it was 4 plus. In 1942 the reaction to the Kahn test was positive.

In 1940 the discharge diagnosis at another hospital was latent syphilis and hypertension. An insurance policy requiring a physical examination was granted in 1943. In January 1944, three days prior to admission, the patient was seen at this hospital's clinic and the blood pressure was 128 systolic and 84 diastolic. When he was admitted the physical examination revealed no abnormalities except in the chest. Dry rales were audible at the bases of both lungs. The heart sounds were of good quality, a soft systolic murmur was audible at the apex and the aortic second sound was accentuated. The heart was not enlarged on fluoroscopic examination. The blood pressure was 200 systolic and 110 diastolic.

Laboratory Data.—The urine had a specific gravity of 1.012 and was cloudy. It gave a 1 plus reaction for albumin and contained no glucose or acetone. The reaction to the benzidine test was positive. Microscopic examination showed many clumped white cells, many red cells and many red blood cell and granular casts. The red blood cell count was 2,500,000, hemoglobin content 8.5 Gm. (55 per cent), and the white blood cell count 9,400. The differential count showed 5 staff forms, 79 segmented forms, 14 small lymphocytes and 2 monocytes. The icterus index was 6.3 and the serum bilirubin content 0.20 mg. per hundred cubic centimeters. The carbon dioxide content was 29 volumes, nonprotein nitrogen 136 mg., calcium 8.8 mg. and whole blood chloride as sodium chloride 540 mg., per hundred cubic centimeters. The plasma protein measured 7.08 Gm. per hundred cubic centimeters, with 4.09 Gm. of albumin and 2.99 Gm. of globulin (ration of 1.37). Spectroscopic examination of the blood serum revealed the presence of hemoglobin. The Wassermann, Kahn and Kline reactions were all positive.

The diagnosis was (1) paroxysmal cold hemoglobinuria due to syphilis resulting in hemoglobinuric nephrosis and azotemia and (2) hypertensive arteriosclerotic heart disease with left ventricular failure.

Course in the Hospital.—A large fluid intake was provided by mouth and was supplemented by the intravenous administration of Hartmann's solution (one-sixth molar sodium lactate). Administration of potassium bicarbonate (2 Gm. four times a day) was started on the second day in the hospital (32 Gm. in all given). Under this regimen the urinary output rose from 750 cc. on the second day in the hospital to 2,300 cc. on the fifth day. The urine was now alkaline (p_H 7.5). The carbon dioxide content rose to 42.6 volumes per cent, but the nonprotein nitrogen level rose to 158 and then to 171 mg. per hundred cubic centimeters. The urine remained clear, the specific gravity never rising above 1.010. The patient was troubled with considerable abdominal distention, which responded poorly to the frequent use of neostigmine and enemas. An electrocardiogram taken on January 18 showed decided left deviation of the electrical axis and intraventricular block; the QRS interval measured 0.12 second. On the same day the Donath-Landsteiner test gave a negative reaction. Sternal marrow aspirated was normal. The blood pressures were as follows: on January 15, 174 systolic and 96 diastolic; on January 17, 174 systolic and 87 diastolic; on January 18, 192 systolic and 84 diastolic.

On the evening of the fifth day in the hospital the patient became severely dyspneic and orthopneic, and moist rales were audible in both pulmonary fields. The usual treatment for acute left ventricular failure with pulmonary edema was instituted, including the use of morphine and rapid digitalization. Despite this therapy, the patient died on the morning of the sixth day.

Postmortem Examination.—Postmortem examination was performed by Dr. Alfred Plaut. The significant observations were limited to the heart, lungs and kidneys. The heart weighed 480 Gm.; the thickness of the left ventricular wall was 22 mm. and that of the right ventricular wall 8 mm. The left auricle and ventricle appeared dilated. The aorta showed moderate arteriosclerotic involvement. There was no evidence of syphilis. The lungs were heavy and contained considerable bloody and foamy fluid on the cut surface. The right kidney weighed 275 Gm. and the left 270 Gm. They were large and heavy, and their capsules stripped with difficulty. The cortex was thick and stained a light brownish red.

Microscopic Report.—The microscopic report on the kidneys was as follows: While the number of glomeruli is decreased, most of them are normal. Some, however, exhibit varying degrees of shrinking, and their capsules are thickened. The capsular spaces throughout are empty. There is moderate diffuse fibrosis throughout the kidney. Areas of more intense fibrosis correspond to those areas in which many tubules are atrophic. The contour of the capsule is somewhat undulating, and there are numerous shallow scars. These scars contain many cells, mostly mononuclear. The majority of these cells are larger than lymphocytes, but there are also many typical lymphocytes.

Except for slight elastosis, which is not unusual at the age of 56, no changes in the blood vessels are detected. There is no pyelitis nor any ascending inflammation. The hilar fat is infiltrated in places with small round cells and large mononuclear elements with rather compact protoplasm. One small hemorrhage is situated near the tip of a pyramid. There is no diffuse inflammatory process.

The primary convoluted tubules are moderately wide. Their lumens contain some indistinct amorphous material. The epithelium of the convoluted tubules contains little fat.

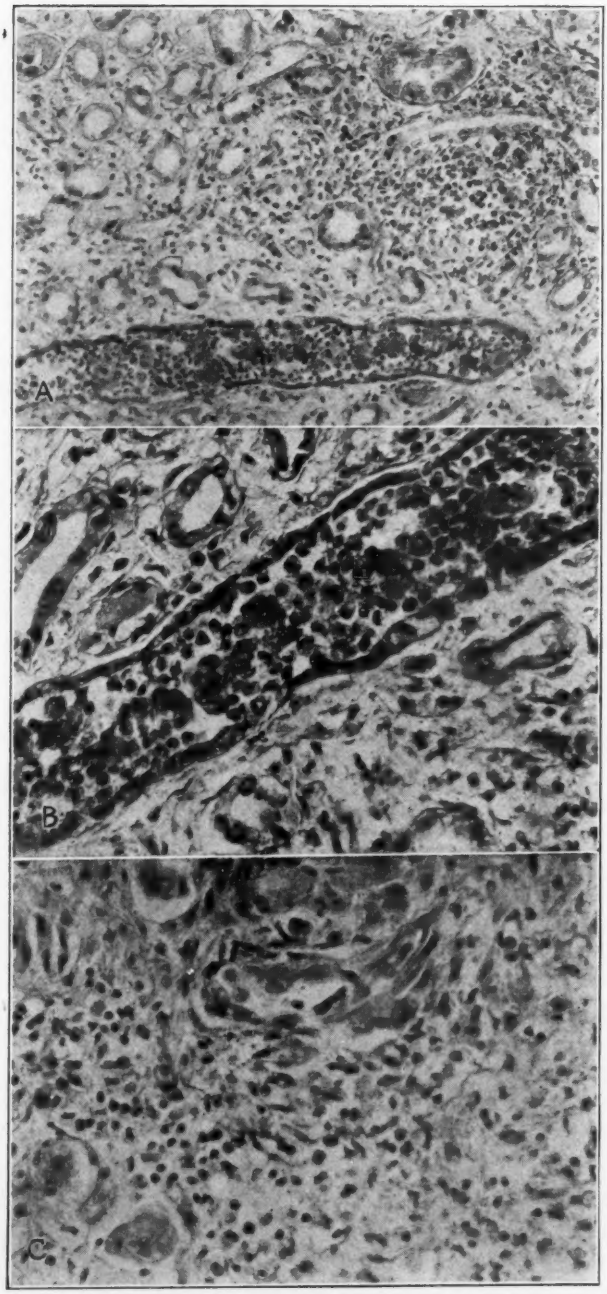

Fig. 1.—*A*, low power view demonstrating collecting tubule filled with pigment and cellular debris and inflammatory focus of round cells and leukocytes; *B*, high power magnification of collecting tubule; *C*, high power magnification of inflammatory focus.

Brownish masses, some amorphous, some finely or coarsely granular and some of larger particles, occupy the lumens of many collecting tubules, of some of Henle's loops and of many distal convoluted tubules. While these masses occasionally resemble erythrocytes in size and shape, they all stain differently from the red blood cells in blood vessels. In spite of continued search, no red blood cells can be demonstrated in the lumens of any renal tubule. In some tubules the lumen is filled with brown masses while the epithelium appears intact, in some the lumen is free and the intact-appearing epithelium is filled with pigment granules and in some the epithelial cells contain pigment granules but their outlines are much distorted. In other tubules the epithelium appears almost entirely destroyed and only the pigment is visible. All gradations among these different phases can be found. There also is an alternation of normal-appearing and of obviously diseased granular epithelial cells in cross sections of tubules in which no pigment is seen.

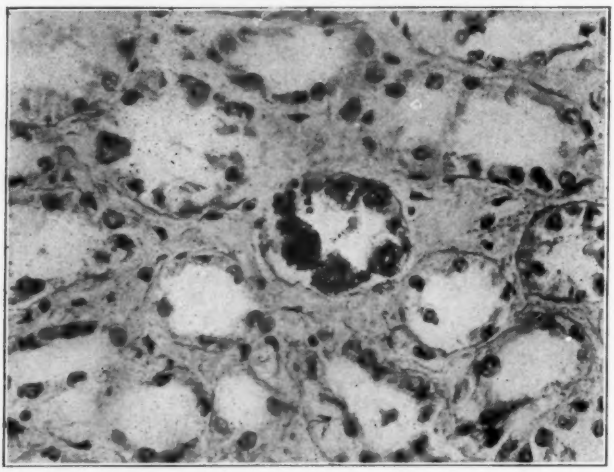

Fig. 2.—View showing many tubules. The center one has pigment granules within an epithelial cell, and cell outlines are much distorted. Above it is a regenerating tubule; below it are several tubules with necrotic epithelium.

The color of the pigment varies from a deep brown to a pale yellowish green. The lighter shades, however, are only seen in the small granules. All the thicker masses appear dark brownish. Independent of the pigment masses, hyaline casts are found, some of which appear pink in the sudan stain.

Inflammatory foci are numerous; in many of these foci a damaged tubule can be recognized in the center. These tubules contain pigment as described. Various degrees of destruction are seen, and in some foci no remnants of the tubules are recognizable. The ratio of leukocytes and mononuclear elements varies. Leukocytes also are present in the lumen of the tubules, generally mingled with masses of pigment and desquamated epithelium. Occasionally, tubules are seen obviously in the process of destruction, but there is no inflammatory reaction in their neighborhood. The inflammatory foci reach 2 mm. in diameter. Small calcific foci are present.

Iron Reaction: The iron reaction (prussian blue) of the glomeruli, the inflammatory foci and the interstitial tissue is negative. The loose masses in the lumen of the primary convoluted tubules give a rather faint iron reaction. The reaction of the pigment masses in the epithelium of the loops of Henle and in the secondary convoluted tubules is strongly positive. The reaction of the masses in the lumen of the large collecting tubules again are positive.

COMMENT

A. *Cause for the Negative Donath-Landsteiner Reaction.*—That this case represents the syndrome of paroxysmal cold hemoglobinuria is apparent from the clinical history, although the Donath-Landsteiner reaction was negative. This reaction is based on the presence of a cold hemolysin circulating in the plasma. If red cells of the same group are added to the plasma containing this hemolysin and the mixture is chilled in ice water and then reheated in the presence of complement, hemolysis occurs. In the performance of the test, only the patient's hemolysin-laden plasma need be used. In the presence of guinea pig complement and any red blood cells of the same blood group, the red blood cells will be hemolyzed. Two stages characterize the hemolytic process. The first is cold fixation of the hemolysin on the erythrocyte at appropriately low temperatures, for which action complement is unnecessary. The second is heat lysis of the already sensitized erythrocytes after they are warmed to 37 C. in the presence of complement. A common identity for this reaction and the Wassermann reaction has been suggested but has been disproved by cold-fixing all the hemolysin in a given blood sample and observing no change in the titer in a subsequently performed Wassermann test, despite the fact that the Donath-Landsteiner reaction becomes negative.

The absorption of all the hemolysin in the cold may well be the explanation of the negative Donath-Landsteiner reaction in this instance, for according to the patient's history this was the most severe and prolonged exposure of the twelve which he had suffered. The severity of the subsequent hemolytic reaction strengthens the conclusion that all the hemolysin was absorbed by the lysed erythrocytes, which left none available in the plasma.[2] The Rosenbach test, in which the patient's feet are immersed in ice water for ten minutes and hemolysis is awaited, was considered a dangerous procedure, although the modification known as the Ehrlich test might have been carried out. In this test localized hemolysis is produced in a finger by arresting venous return with a ligature tied at the base of the finger and immersing the finger in ice water. The presence of free hemoglobin in the heated serum collected from the chilled digit documents a hemolytic reaction occurring in the cold.

2. Rosen, S. F.: Paroxysmal Hemoglobinuria with Case Report, South. M. J. **26**:1038-1044, 1933.

Since all these tests depend on the availability of cold hemolysin, it is likely that none of them would have been helpful in identifying the cause of the hemoglobinuria because of the probable absorption of all the available hemolysin.

B. *Relation to Post-Transfusion and Crush Injury Nephrosis.*—The manner in which this patient died with evidence of renal insufficiency reveals an arresting similarity to post-transfusion renal reactions which occur after large quantities of incompatible blood have been injected. The precise mechanism by which hemoglobin damages the kidney in these instances has engaged the attention of numerous investigators.[3] The result of their studies indicates that the healthy kidney is well able to cope with free hemoglobin when the plasma level is low, in which instance it behaves like other threshold substances, traversing the glomerular filter and then undergoing reabsorption in the tubule and not appearing in the urine.[4] Such a state of affairs apparently exists up to levels of 135 mg. of hemoglobin per hundred cubic centimeters of plasma.[5] When the hemoglobin leaves the erythrocytes and attains a plasma level in excess of 135 mg., it is excreted in the urine because the tubular capacity for hemoglobin reabsorption has been reached and the tubule cells are incapable of handling increased amounts of that protein delivered in the glomerular filtrate. An interesting observation on the threshold level of hemoglobin reveals that once the tubular cells are loaded with iron pigment their continued ability to reabsorb hemoglobin is diminished and is reflected by a fall in

3. (*a*) Baker, S. L., and Dodds, E. C.: Obstruction of the Renal Tubules During Excretion of Hemoglobin, Brit. J. Exper. Path. **6**:247-260, 1925. (*b*) De Gowin, E. L.; Warner, E. D., and Randall, W. L.: Renal Insufficiency from Blood Transfusions: Anatomic Changes in Man Compared with Those in Dogs with Experimental Hemoglobinuria, Arch. Int. Med. **61**:609-630 (April) 1938. (*c*) De Navasquez, S.: Excretion of Haemoglobin, with Special Reference to "Transfusion" Kidney, J. Path. & Bact. **51**:413-425, 1940. (*d*) Foy, H.; Altman, A.; Barnes, H. D., and Kondi, A.: Anuria, with Special Reference to Renal Failure in Blackwater Fever, Incompatible Transfusions, and Crush Injuries, Tr. Roy. Soc. Trop. Med. & Hyg. **36**:197-238, 1943. (*e*) Flink, E. B.: Blood Transfusion Studies: III. The Relationship of Hemoglobinemia and of the p_H of the Urine to Renal Damage Produced by Injection of Hemoglobin Solutions into Dogs, J. Lab. & Clin. Med. **32**:223-261, 1947. (*f*) Goldring, W., and Graef, I.: Nephrosis with Uremia Following Transfusion with Incompatible Blood: Report of Seven Cases with Three Deaths, Arch. Int. Med. **58**:825-845 (Nov.) 1936.

4. Ottenberg, R., and Fox, C. L., Jr.: The Rate of Removal of Hemoglobin from the Circulation and the Renal Threshold in Human Beings, Am. J. Physiol. **123**:516-525, 1938.

5. Gilligan, D. H.; Altschule, M. D., and Katersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, J. Clin. Investigation **20**:177-187, 1941.

the renal threshold of hemoglobin by as much as 60 per cent.[6] Thus, repeated episodes of hemoglobinemia occurring at short intervals are more apt to be attended by hemoglobinuria than is an initial episode of more extensive intravascular hemolysis. That the height of the hemoglobin level attained in the plasma is the chief factor in determining renal insufficiency is indicated by the recent report of Flink,[3e] who observed serious renal insufficiency in all dogs in which the plasma values for hemoglobin exceeded 3.7 Gm. per hundred cubic centimeters immediately after completion of the injection of hemoglobin. Similarly, Foy and Kondi[7] observed obliguria and anuria in human beings with the highest levels of plasma hemoglobin during blackwater fever.

It is surprising that the giant size of the hemoglobin molecule (68,000) is not an absolute deterrent to its passage through the glomerular filter; its clearance is 3 per cent of that of creatinine, a substance which in the dog is a measure of glomerular filtration since it is not reabsorbed by the tubules. Lichty, Havill and Whipple[6e] suggested that only 3 per cent of the glomerular pores are large enough to permit the passage of this large hemoglobin molecule. The appearance of methemalbumin[8] a highly toxic substance, in the plasma, is the herald of extensive hemolysis and is indicative of plasma hemoglobin levels in the neighborhood of 300 to 500 mg. per hundred cubic centimeters.

Myoglobin, another protein closely related to hemoglobin, whose molecular weight is only one-fourth (17,500) that of the latter, is observed in the urine of persons dying of renal insufficiency as a result of muscle destruction, with a clinical and pathologic picture often indistinguishable from the renal necrosis resulting from mismatched transfusion.

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6. (*a*) Yuile, C. L.: Hemoglobinuria, Physiol. Rev. **22**:19-31, 1942. (*b*) Monke, J. V., and Yuile, C. L.: Renal Clearance of Hemoglobin in Dog, J. Exper. Med. **72**:149-165, 1940. (*c*) Bogniard, R. P., and Whipple, G. H.: Iron Content of Blood Free Tissues and Viscera: Variations Oue to Diet, Anemia and Hemoglobin Injections, ibid. **55**:653-665, 1932. (*d*) Yuile, C. L.; Steinman, J. F.; Hahn, P. F., and Clark, W. F.: The Tubular Factor in Renal Hemoglobin Excretion, ibid. **74**:197-202, 1941. (*e*) Lichty, J. A., Jr.; Havill, W. H., and Whipple, G. H.: Renal Thresholds for Hemoglobin in Dogs: Depression of Threshold Due to Frequent Hemoglobin Injections and Recovery During New Periods, ibid. **55**:603-615, 1932.

7. Foy, H., and Kondi, A.: Blackwater Fever in Macedonia, Tr. Roy. Soc. Trop. Med. & Hyg. **31**:123-138, 1937; Spectroscopic Analysis of Pigments in Serum and Urines of Blackwater Fever, ibid. **32**:49-65, 1938.

8. Fairley, N. H., and Bromfield, R. J.: Laboratory Studies in Malaria and Blackwater Fever: New Blood Pigment in Blackwater Fever and Other Biochemical Observations, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:307-334, 1934.

The recent air war enabled the British to study cases of crush injury and myoglobinuria with great care. It is significant that most of the deaths occurred on the sixth day following injury, after signs of shock had disappeared, and usually climaxed progressive renal impairment during which blood pressures rose and azotemia developed. Observations on the renal insufficiency following transfusions are strikingly similar since most of the reported deaths occurred seven to ten days after the initiating hemolytic accident.

Trauma is unnecessary for the production of the syndrome, since Haff disease,[9] cases of which were reported from Königsberg, and acute paralytic myoglobinuria[10] may produce completely similar clinical patterns.

During the onset of crush injury,[11] the urine is generally highly acidic, with a p_H of 4.5, containing acid hematin crystals. As time goes on, fixation of the specific gravity occurs despite the presence of a diminishing urinary volume. An inverse ratio between the urea and the chloride in the plasma and blood is observed, the urea content being high in the plasma and the chloride content low. Potassium and creatinine levels are high in the initial urine voided. The fatalities occurring are suggestive of fatal potassium poisoning, with death from cardiac impairment, since the electrocardiogram discloses increased height of the T waves and disturbances in intraventricular conduction.

C. *Elements Producing Renal Tubular Necrosis (Experimental Observations).*—Experimental studies are helpful in analyzing the mechanism of tubular injury in these instances. Important among them is the work of Yuile and others,[12] who showed that ischemia or previous tartrate injury rendered the renal tubules of rabbits more susceptible to destruction. It should be recalled that in 1937 Fishberg stressed the basic nature of the diminished circulating blood volume and the decreased renal blood flow as a cause of the renal impairment accompanying prerenal azotemia in a great variety of circumstances.[13] Since that

9. Ross, J. F.: Medical Progress: Hemoglobinemia and the Hemoglobinurias, New England J. Med. **233**:766, 1945.

10. Bywaters, E. G. L., and Dible, J. H.: Acute Paralytic Myohaemoglobinuria in Man, J. Path. & Bact. **55**:7-15, 1943.

11. Bywaters, E. G. L., and Beall, D.: Crush Injuries with Impairment of Renal Function, Brit. M. J. **1**:427-432, 1940. Bywaters, E. G. L.: Ischemic Muscle Necrosis: Crushing Injury, Traumatic Edema, Crush Syndrome, Traumatic Anuria, Compression Syndrome; a Type of Injury Seen in Air Raid Casualties Following Burial Beneath Débris, J. A. M. A. **124**:1103-1109 (April 15) 1944.

12. Yuile, C. L.; Gold, M. A., and Hinds, E. S.: Hemoglobin Precipitation in Renal Tubules: A Study of Its Causes and Effects, J. Exper. Med. **82**:361-374, 1945.

(Footnotes continued on next page)

time it has been recognized that during shock, hemorrhage and vasoconstriction renal necrosis may occur without the intervention of any other mechanism, being solely a result of tubular anoxia.[14]

Trueta and his colleagues [15] have recently demonstrated how renal cortical blood flow may be short-circuited by neural impulses in the rabbit, producing an almost pure subcortical or medullary renal circulation with consequent decrease in glomerular filtration and impaired tubular function. These were evidenced by oliguria and the arterial quality of the bright red blood entering the renal vein. Similarly, widespread vasoconstriction which occurs in the course of posthemorrhagic, postoperative and posthemolytic states is associated with a decrease in circulating blood volume and diminished renal blood flow leading to tubular anoxia which is evidenced by oliguria and often anuria. An element of tubular anoxia is thus seen to be an integral part of the renal impairment accompanying transfusion reaction and crush injury.

Smith's [16] suggestion that the reabsorption of water is divided into obligatory and facultative areas of the renal tubular apparatus completes the explanation for the mechanism of injury in hemoglobinuric necrosis. According to his view, which is based on the studies of Walker and others,[17] Shannon [18] and Verney,[19] 85 per cent of the glomerular filtrate is reabsorbed in the proximal tubular segment of the nephron, whereas 15 per cent is the responsibility of the distal tubule and the thin limb of Henle's loop under the influence of the antidiuretic hormone of the neurohypophysis. The concentrating activity which creates a hypertonic urine apparently resides in the lower nephron.

It is during the early phases of hemoglobin excretion, while there is still functional tubular integrity, that this concentrating process

13. Fishberg, A. M.: Prerenal Azotemia and Pathology of Renal Blood Flow, Bull. New York Acad. Med. **13**:710-732, 1937.

14. Maegraith, B. G.; Havard, R. E., and Parsons, D. S.: Renal Syndrome of Wide Distribution Induced Possibly by Renal Anoxia, Lancet **2**:293-296, 1945. Tomb, J. W.: Anuria and Anoxia, J. Trop. Med. **45**:125, 1942.

15. Trueta, J.; Daniel, P.; Barclay, A. E.; Franklin, K. S., and Prichard, M. M. L.: Renal Pathology in the Light of Recent Neurovascular Studies: Preliminary Communication, Lancet **2**:237-238, 1946.

16. Smith, H. W.: The Excretion of Water, Bull. New York Acad. Med. **23**:177-195, 1947.

17. Walker, A. M.; Bott, P. A.; Oliver, J., and MacDowell, M. C.: Collection and Analysis of Fluid from Single Nephrons of Mammalian Kidney, Am. J. Physiol. **134**:580-595, 1941.

18. Shannon, J. A.: Control of Renal Excretion of Water: Effect of Variations in State of Hydration on Water Excretion in Dogs with Diabetes Insipidus, J. Exper. Med. **76**:371-386, 1942.

19. Verney, E. B.: Absorption and Excretion of Water, Lancet **2**:739-781. 1946.

may damage the vital function of the cells of the lower nephron by exposing them to high concentrations of hemoglobin, unattainable in the proximal nephron. While small amounts of protein are apparently constantly passing through the glomerulus and being reabsorbed, larger quantities are alien to the vertebrate tubule.[20] The persistence of some forms of proteinuria is eventually associated with renal tubular destruction, as observed with Bence Jones proteosuria, as well as with the excretion of certain globulins.[21]

Studies of renal impairment accompanying multiple myeloma carried out by one of us (R. M. S.) have disclosed renal insufficiency in all cases in which the serum globulin exceeded 10 Gm. per hundred cubic centimeters. A recent report of a case of renal insufficiency associated with Boeck's sarcoid[22] similarly revealed elevation of the serum globulin level. This problem is still under investigation.

It is our view that the proteins hemoglobin and myoglobin in high concentration are toxic to the lower nephron; they or their degradation products are injurious to the distal tubular segment because hypertonic concentration resides in this renal region. Vasoconstriction and diminished renal blood flow produce tubular anoxia and increase tubular susceptibility to such injury.

An exhaustive and stimulating study of lower nephron nephrosis by Lucké[23] considers this among other possibilities. At the present time there is no cogent evidence which indicates that alkaline therapy is useful once hemolysis has occurred. Indeed fatal reactions have occurred in the presence of persistently alkaline urine.

The manner in which the patient described here died, in left ventricular failure, suggests a cardiac as well as a renal element as the cause of death. The terminal oliguria frequently observed in cases of mismatched transfusion and crush injury was lacking. It is thought that the immediate cause of death may have been the high level of potassium produced by the antiacidosis regimen of potassium bicarbonate instituted because of the concomitant presence of heart failure, during

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20. Dock, W.: Proteinuria and Associated Renal Changes (Evans Lecture), New England J. Med. **227**:633-636, 1942. Ekehorn, G.: Principles of Renal Function, Acta med. Scandinav., 1931, supp. 36, pp. 1-717. Bott, P. A., and Richards, A. N.: The Passage of Protein Molecules Through the Glomerular Membranes, J. Biol. Chem. **141**:291-310, 1941.

21. Blackman, S. S., Jr., and Davis, B. D.: Electrophoretic and Chemical Analysis of Protein in Nephritic Urine, J. Clin. Investigation **22**:545-549, 1943.

22. Klinefelter, H. F., Jr., and Salley, S. M.: Sarcoidosis Simulating Glomerulonephritis, Bull. Johns Hopkins Hosp. **79**:333-341, 1946.

23. Lucké, B. L.: Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons), Mil. Surgeon **99**:371-396, 1946.

which sodium ion is ordinarily withheld. This induced rise in serum potassium level paralleled the increase ordinarily seen in fatal cases of crush injury in which death is usually due to cardiac impairment with evidences of potassium poisoning resulting in the high T waves and the conduction disturbances observed in the electrocardiogram. The disturbance in ventricular conduction observed in the electrocardiogram of this patient may well have been due to hyperpotassemia. The frequent use of neostigmine may also have exercised a potassium effect on the cardiac muscle because of the rise in the local potassium level following the administration of cholinergic drugs.

The pathologic findings were interesting in that they revealed evidence of fresh and old tubular disease, with signs of an old inflammatory renal process as indicated by the thickening and adhesions of the

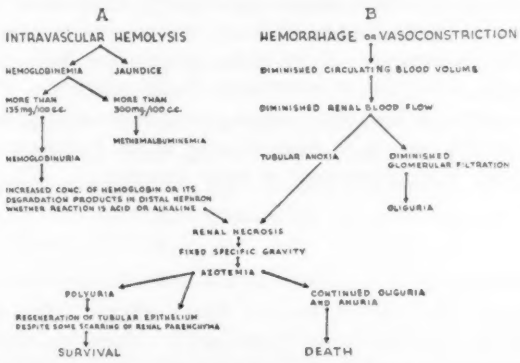

Fig. 3.—Scheme illustrating the mechanism of renal injury accompanying most cases of intravascular hemolysis. Note that renal necrosis is a result of varying combinations of factors *A* and *B*, that polyuria usually heralds improvement and continued oliguria or anuria indicates a fatal outcome and that acidification or alkalinization is not crucial to hemoglobin precipitation and tubular injury.

capsule, a diffuse fibrotic process with numerous scars and mononuclear infiltrates. The last were apparently remnants of renal injury resulting from eleven previous hemolytic episodes. It should be noted that no vascular changes were reported to suggest a vascular cause for the renal lesions.

The anatomic evidence thus supports the notion that progressive renal injury with final functional impairment results from repeated hemolytic episodes and that although tubular regeneration may be adequate to prevent renal decompensation in the initial attacks the destructive process finally damages so much renal tissue that there can be no return to adequate function. The same view may be applied to other forms of renal necrosis.

It is suggested that the patient's sudden death in left ventricular failure was related to the retention of serum potassium in the presence of renal insufficiency resulting from repeated intravascular hemolyses due to cold exposure.

SUMMARY

1. A fatal case of renal tubular necrosis resulting from twelve attacks of paroxysmal cold hemoglobinuria is presented.

2. The anatomic observations reflected old and recent renal injury apparently due to hemolytic episodes.

3. The use of potassium salts for alkalinization is thought to be responsible for the mode of death.

4. The mechanism of renal necrosis accompanying paroxysmal cold hemoglobinuria, mismatched transfusion and crush injury is viewed as a result of tubular anoxia secondary to diminished circulating blood volume and toxic damage of the epithelium of the lower nephron by excessive concentrations of the globin proteins or their degradation products during hypertonic concentration of the urine.

5. Repeated single hemolytic episodes associated with hemoglobinuria may each occasion quanta of renal damage which eventuate in significant and finally fatal impairment of renal function.

JARISCH-HERXHEIMER REACTION IN NEUROSYPHILIS TREATED WITH PENICILLIN

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IN NEUROSYPHILIS an early reaction to the administration of spirocheticidal drugs (the Jarisch-Herxheimer reaction) may take one or both of two forms: a transient rise in temperature during the first twenty-four hours after administration of the drug or an exacerbation of mental symptoms or neurologic signs during the first few days.

Febrile reactions have been observed after the administration of arsenical drugs, bismuth and, more recently, penicillin. The literature contains only brief comments concerning the incidence and severity of fever after the use of these drugs.

Symptomatic Herxheimer reactions occur not only after the administration of spirocheticidal drugs but also during fever therapy (especially induced malaria). The variety of manifestations observed is related to the type of neurosyphilis. For example, in patients with dementia paralytica there may occasionally occur exacerbations of the existing psychoses or the development of new symptoms. Confusion, agitation, hallucinations and convulsions may sometimes develop. In persons with tabes dorsalis lightning pains and urinary difficulties may be temporarily intensified during treatment or may appear for the first time. The initiation of treatment has been reported to precipitate agitation or confusion even in patients with asymptomatic neurosyphilis.

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This paper presents data concerning the Herxheimer reaction in patients with neurosyphilis given penicillin therapy. Febrile and symptomatic reactions to penicillin may occur during the treatment of both early and late syphilis, including most types of neurosyphilis. Such reactions have not been reported during the use of penicillin for other infections involving the nervous system or for a wide variety of acute systemic infections. Neither have they been observed after administration of procaine penicillin G (100 to 500 units per kilogram) to 40 male and female patients with gonorrhea.[1] In this group, rectal temperatures were recorded at hourly intervals for twenty-four hours.

The present study is based on an investigation of 349 afebrile patients with neurosyphilis who were treated with aqueous penicillin alone at the Johns Hopkins Hospital between 1944 and 1948. Initial doses of penicillin ranging from 30,000 to 300,000 Oxford units were administered intramuscularly within the first six hours. Rectal temperatures were recorded every two to four hours. A febrile reaction was arbitrarily defined as a rise in temperature above 100 F. (37.8 C.). We are here concerned primarily with the febrile response and only secondarily with symptomatic reactions. No attempt is made to compare Herxheimer reactions observed during penicillin therapy with those observed during other methods of treatment.

RESULTS

1. *Incidence of Febrile Reactions.*—Febrile reactions have been previously reported in 13 to 54 per cent of adult patients treated for various types of neurosyphilis with commercial penicillin.[2] In the present series of 349 patients the total incidence was 34 per cent (table 1). Fever occurred after administration of commercial penicillin in 35 per cent (76 of 216 patients) and after administration of crystalline penicillin G [3] in 32 per cent (43 of 133 patients). Since

1. Unpublished data.

2. (*a*) Stokes, J. H.; Sternberg, T. W.; Schwartz, H.; Mahoney, J. F.; Moore, J. E., and Wood, W. B., Jr.: The Action of Penicillin in Late Syphilis, J. A. M. A **126**:73-79 (Sept. 9) 1944. (*b*) Koteen, H.; Doty, E. J.; Webster, B., and McDermott, W.: Penicillin Therapy in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **31**:1-13 (Jan.) 1947. (*c*) Callaway, J. L.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, ibid. **30**:100-124 (March) 1946. (*d*) Tucker, H. A., and Robinson, R. C. V.: Neurosphilitic Patients Treated with Penicillin: Probable Herxheimer Reactions, J. A. M. A. **132**:281-283 (Oct. 5) 1946. (*e*) Moore, J. E.: Penicillin in Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1947.

3. The crystalline penicillin G used in these studies was supplied by the Commercial Solvents Company, lot numbers 46042605 and 46082605. The potency was 1,500 to 1,540 units per milligram.

incidence was not related to the type of penicillin, the two groups are combined in all analyses except those relating to dosage.

No significant race or sex differences in the incidence of reactions were demonstrated (table 1).

2. *Incidence of Symptomatic Reactions.*—The number of patients with early symptomatic reactions in previously reported series has varied from 8 to 11 per cent of those treated.[4] Among the 349 persons in this series significant aggravations of mental symptoms or neurologic signs during the first one to six days of treatment occurred in only 6 (1.7 per cent). Two of these patients have been previously reported on.[2d] The symptoms or signs observed in the 6 patients were convulsions in 2 instances, confusion and disorientation in 2, hallucinations and delusions in 1 and signs of meningeal irritation in 1. All patients had associated febrile reactions. In 4 patients the original diag-

TABLE 1.—*The Relationship of the Incidence of Febrile Reactions After Administration of Penicillin to the Race and Sex of Patients with Neurosyphilis*

	Number Treated	Febrile Reactions	
		Number	Percentage
Race			
White	115	35	30
Negro	234	84	36
Sex			
Male	235	82	35
Female	114	37	32
Total	349	119	34

nosis was dementia paralytica (an incidence of 7.3 per cent for this diagnostic group) and in 2 asymptomatic neurosyphilis (1.4 per cent). No reactions were noted in patients with other forms of neurosyphilis. However, it is possible that exacerbations of such complaints as lightning pains may not have been recorded. The 2 patients with asymptomatic neurosyphilis and 1 of those with dementia paralytica had only transient symptoms, with no recurrence during the next two to three years. The other 3 patients, who had been recognized as having advanced dementia paralytica before treatment was commenced, were committed to mental institutions. One of these showed sufficient improvement to allow discharge from the hospital after three months. The other 2 required custodial care for periods of nine and thirty months respectively.

4. Gammon, G. D.; Stokes, J. H.; Steiger, H. P.; Steele, W. H.; Beerman, H.; Ingraham, N. R., Jr.; Gyorgy, P.; Rose, E., and Lentz, J. W.: Penicillin Therapy Alone in Neurosyphilis: An Analysis of Clinical Results, Ann. Int. Med. **25**:412-432 (Sept.) 1946. Stokes and others.[2a] Callaway and others.[2c]

TABLE 2.—*The Relationship of the Incidence of Febrile Reactions to the Stage and Type of Neurosyphilis*

Diagnostic Type	Stage	Number Treated	Febrile Reactions	
			Number	Percentage
Acute syphilitic meningitis	Early	17	4	24
Asymptomatic	Early and late	136	33	24
Meningovascular	Early and late	78	28	36
Dementia paralytica and dementia paralytica with tabes	Late	55	41	74
Tabes dorsalis, with or without primary optic atrophy	Late	40	9	23
Other types	Late	23	4	17
Total		349	119	34

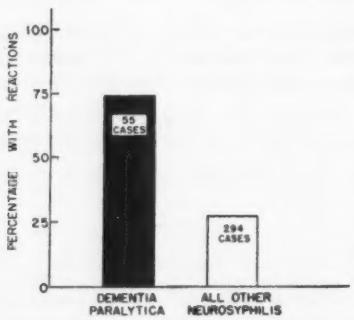


Fig. 1.—Relationship of the incidence of early febrile reactions to the diagnostic type of neurosyphilis.

3. *Relationship to the Duration of Syphilitic Infection and to the Diagnostic Type of Neurosyphilis.*—In contrast with the low incidence of febrile reactions to penicillin reported for most forms of neurosyphilis, a higher incidence of 64 to 79 per cent has been reported for dementia paralytica.[5] The present series, which includes 41 cases of dementia paralytica previously reported from this clinic,[5a] amplifies this observation.

The occurrence of febrile reactions according to the stage and type of neurosyphilis is presented in table 2 and figure 1. There is no relationship between incidence and duration of infection. In all types of neurosyphilis except dementia paralytica febrile reactions occurred in 17 to 36 per cent of the cases. However, in patients with dementia

5. (*a*) Reynolds, F. W.; Mohr, C. F., and Moore, J. E.: Penicillin in the Treatment of Neurosyphilis: II. Dementia Paralytica, J. A. M. A. **131**:1255-1260 (Aug. 17) 1946. (*b*) Callaway and others.[2c]

TABLE 3.—*Relationship of the Incidence of Febrile Reactions to the Abnormalities of the White Blood Cell Count and the Protein Content of the Cerebrospinal Fluid*

White Blood Cell Count and Protein Content	Dementia Paralytica			Other Types of Neurosyphilis			Total		
	No. of Cases	Febrile Reactions		No. of Cases	Febrile Reactions		No. of Cases	Febrile Reactions	
		No.	%		No.	%		No.	%
Both normal	7	1	14	46	5	10	53	6	11
Cells or protein increased	17	11	64	87	17	19	104	28	26
Both increased	31	29	93	161	56	34	192	85	44

paralytica a definitely increased incidence was observed. Febrile reactions occurred in 41 (74 per cent) of 55 patients with this type.

4. *Relationship to Abnormalities of the Cerebrospinal Fluid.*—The incidence of febrile reactions was studied in relation to the white blood

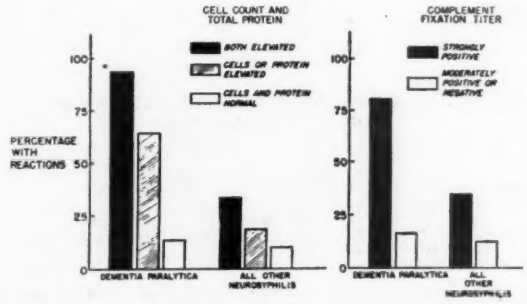


Fig. 2.—Relationship of the incidence of febrile reactions to the abnormalities in the cerebrospinal fluid.

cell count and the total protein content, and also to the titer of reaction in the complement fixation test of the fluid. For the purpose of this study, we have arbitrarily regarded a white blood cell count of 10 or more or a protein content of 40 mg. or more per hundred cubic centimeters as abnormal. Complement fixation titers of 0.2 to 1.0 cc. have been defined as indicative of moderately positive reactions and those of 0.01 to 0.1 cc. as indicative of strongly positive reactions.

The results presented in table 3 and figure 2 show that the frequency of reactions increased directly with increases in white blood cell count and total protein irrespective of the titer of the complement fixation test. This increase was more notable in patients with dementia paralytica but was also seen to a lesser extent in patients with other types of neurosyphilis. The highest incidence (93 per cent) was observed in patients who had dementia paralytica and in whom both the cell count and the protein content were abnormal.

When incidence was related to the titer of the reaction in the complement fixation test, to the exclusion of increased white blood cell counts and protein contents, it was observed that the more strongly positive was the reaction to the test the more frequent were febrile reactions. This was true for all types of neurosyphilis, but especially for dementia paralytica (table 4 and fig. 2).

Table 5 further illustrates these relationships.

TABLE 4.—*Relationship of the Incidence of Febrile Reactions to the Complement Fixation Titer of the Cerebrospinal Fluid*

Reaction to Complement Fixation Test	Dementia Paralytica			Other Neurosyphilis			Total		
	No. of Cases	Febrile Reactions		No. of Cases	Febrile Reactions		No. of Cases	Febrile Reactions	
		No.	%		No.	%		No.	%
Negative or moderately positive	6	1	16	114	15	13	120	16	13
Strongly positive	49	40	81	180	63	35	229	103	42

TABLE 5.—*Relationship of the Incidence of Febrile Reactions to Abnormalities of the Cerebrospinal Fluid*

Cerebrospinal Fluid		Dementia Paralytica			Other Types of Neurosyphilis			Total		
Reaction to Complement Fixation Test	White Blood Cell Count and Protein Content	No. of Cases	Febrile Reactions		No. of Cases	Febrile Reactions		No. of Cases	Febrile Reactions	
			No.	%		No.	%		No.	%
Negative	Both normal	0	0	0	10	1	10	10	1	10
Moderately positive	Both normal	2	0	0	32	3	9	34	3	9
	Cells or protein increased	3	0	0	43	6	14	46	6	13
	Both increased	1	1	..	29	5	17	30	6	20
Strongly positive	Both normal	5	1	20	4	1	25	9	2	22
	Cells or protein increased	14	11	79	44	11	25	58	22	38
	Both increased	30	28	93	132	51	39	162	79	49
Total		55	41	74	294	78	27	349	119	34

5. *Relationship to Serologic Tests for Syphilis.*—There was no correlation of the incidence of febrile reactions with serologic negativity or with the height of the serologic titer.

6. *Relationship to Previous Treatment.*—Among 107 patients never previously treated, febrile reactions occurred in 41 (37 per cent). Of 87 patients who had received metal chemotherapy within a year of the administration of penicillin, 28 (32 per cent) had reactions. Of 14 patients in whom therapeutic malaria had been induced from two months to several years before administration of penicillin, only 1 had a

febrile reaction. Of 9 patients who had received previous courses of penicillin, 2 had reactions.

7. Relationship to Dosage.—Febrile reactions have been observed after administration of as little as 1,000 Oxford units of penicillin.[6] In order to obtain detailed information concerning the incidence of reactions in patients with neurosyphilis in relation to the size of the initial dose, 202 patients treated with varying doses of crystalline penicillin G were studied. The initial doses administered intramuscularly varied from 10 to 20,000 Oxford units of penicillin per kilogram of body weight (table 6). In each of these dosage groups the percentage of patients with decidedly abnormal cerebrospinal fluid and/or dementia paralytica was approximately the same.

The incidence of febrile reactions after varying doses of penicillin (20 to 20,000 Oxford units per kilogram) ranged from 25 to 32 per

TABLE 6.—*The Relationship of the Incidence of Febrile Reactions to the Dosage of Crystalline Penicillin G Administered to 202 Patients with Neurosyphilis*

Penicillin Dosage Given in First Six Hours		Patients Treated	Febrile Reactions	
Mg./Kg.	Units/Kg.		Number	Percentage
13.3	20,000 *	8	2	25
1.67 to 3.33	2,500 to 5,000 †	133	43	32
0.013 to 0.027	20 to 40 *	47	12	26
0.007	10 *	14	0	0

* Single dose only in first forty-eight hours.
† Therapeutic doses repeated every three hours.

cent, with no definite trend in relation to dosage. However, when doses of penicillin as small as 10 Oxford units per kilogram were given, reactions were no longer observed. One of us has shown [7] that the minimal dose producing a reaction in patients with early syphilis (10 units per kilogram) is approximately the same as that required to produce a reaction in patients with neurosyphilis.

8. Pattern of Fever.—The pattern of the febrile response in neurosyphilis was studied among the 119 patients with reactions. The average temperature curve in this group is shown in figure 3, along with the curve previously observed in a study of patients with early syphilis.[7]

In this group of patients with neurosyphilis the earliest elevation of temperature occurred four hours after the first injection. In approximately 20 per cent the maximal elevations were recorded between six to

6. Olansky, S.: The Herxheimer Reactions of Relatively Small Doses of Penicillin, Ven. Dis. Inform. **28**:26-27 (Feb.) 1947.

7. Farmer, T. W.: The Herxheimer Reaction in Early Syphilis Treated with Crystalline Penicillin G, J. A. M. A., **158**:480-485 (Oct. 16) 1948.

ten hours, in 50 per cent between twelve and sixteen hours and in 30 per cent between eighteen and twenty-four hours after injection. Thus, in the temperature curve for neurosyphilis there is an average rise to about 100 F. (37.8 C.) extending over a period of ten hours. Approximately 75 per cent of the patients had temperatures above this sixteen hours after the injection of penicillin. In the majority of instances the temperature remained above 100 F. for four to ten hours. The individual elevations of temperature varied from 100.0 to 104.2 F.

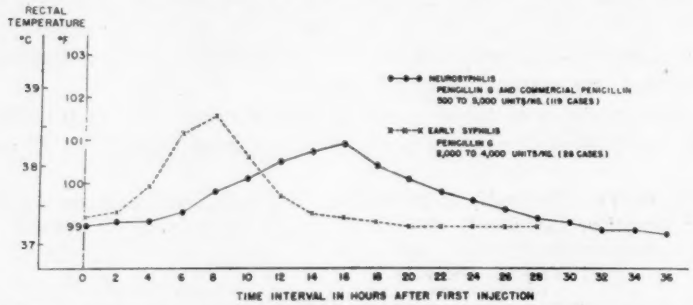


Fig. 3.—Average febrile reactions following the use of penicillin in neurosyphilis and in early syphilis.

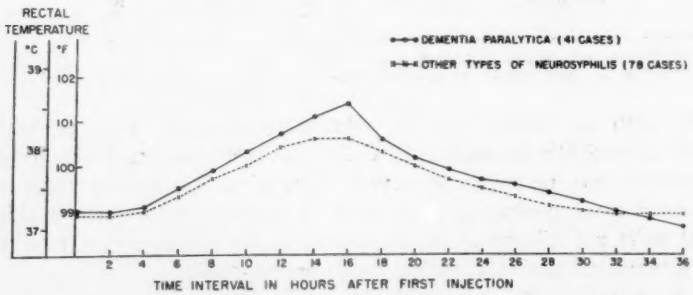
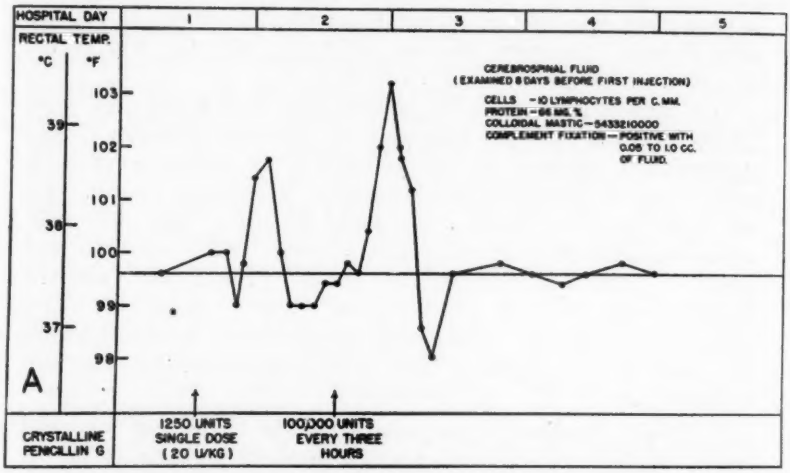


Fig. 4.—Average febrile reactions following the use of penicillin in dementia paralytica and in other types of neurosyphilis.

(37.8 to 40.1 C.), with an average of 100.9 F. (38.3 C.). All patients again had normal temperatures within thirty-six hours after the first injection.

The average febrile reaction to penicillin in patients with early syphilis, which reaches a maximum eight hours after injection and returns to normal by sixteen hours, is contrasted in figure 3 with the slower response in patients with neurosyphilis.

The temporal patterns of febrile response were similar in all the diagnostic types of neurosyphilis. The average temperature curve for



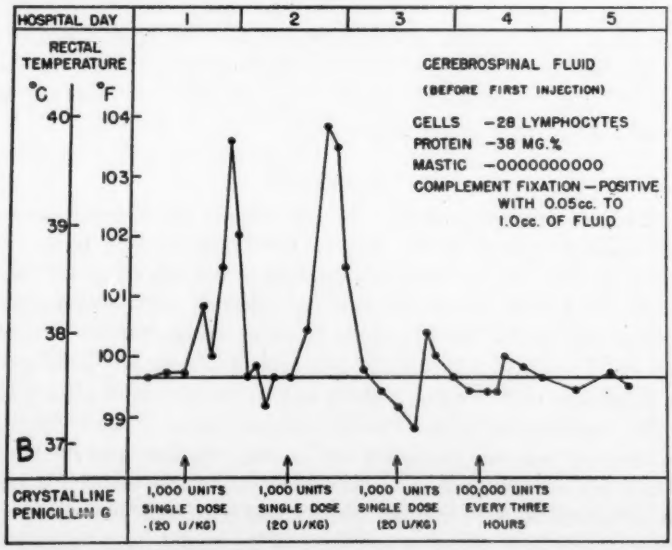


Fig. 5.—*A*, double febrile reaction following the use of crystalline penicillin G in a patient with dementia paralytica; *B*, multiple febrile reactions following the use of crystalline penicillin G in a patient with late asymptomatic neurosyphilis.

dementia paralytica is presented in figure 4 for comparison with that for other types of neurosyphilis. The maximal average temperature in each group was reached sixteen hours after injection. In patients with dementia paralytica this was 101.4 F. (38.6 C.) and in the remainder of the group 100.6 F. (38.1 C.).

The pattern of fever in 43 patients given usual therapeutic doses (2,500 to 5,000 units per kilogram) of crystalline penicillin G was approximately the same as that observed in 12 patients given small initial doses (20 to 40 units per kilogram). The earliest onset of fever was four hours after injection in each of the two groups. The individual maximum elevations of temperature were 103.2 F. (39.6 C.) and 103.8 F. (39.9 C.) in these two groups. The average maximal elevations were 101.0 F. (38.3 C.) and 101.2 F. (38.4 C.). This similarity in the pattern of fever in response to small doses and also to therapeutic doses of penicillin in the same patient is further illustrated in figure 5 *A*.

9. *Double Herxheimer Reactions.*—Of the 12 patients who had shown febrile reactions to small single doses of penicillin (table 6), fever again developed in 9 when they were given either a therapeutic dose or a repeated small dose of penicillin twenty-four to seventy-two hours later. This double Herxheimer reaction is illustrated in figure 5 and is essentially the same as that observed in cases of early infectious syphilis. Repetition of the febrile response was not observed after repeated large single doses of penicillin.

COMMENT

We have demonstrated that the Herxheimer phenomenon occurs in approximately one third of patients with neurosyphilis treated with penicillin. The incidence of this reaction is not related to the race or sex of the patient, to the duration of infection with syphilis, to the serologic titer of the blood or to the penicillin dosage (above a threshold level of 20 units per kilogram). However, it is definitely influenced by the diagnostic type of neurosyphilis and by the degree of abnormalities in the cerebrospinal fluid. Febrile reactions occur in three fourths of the cases of dementia paralytica but in only one fourth of the cases of other types of neurosyphilis. The occurrence of this reaction is related also indirectly to the increased white blood cell count and total protein content and to the degree of positivity of the complement fixation reaction in the cerebrospinal fluid. However, two observations suggest that the character and degree of the abnormalities of the fluid are by no means the sole influencing factors. First, among 17 patients with acute syphilitic meningitis and with pronounced abnormalities in the fluid only 4 had reactions. Second, among patients with early syphilis

the presence or absence of abnormalities in the cerebrospinal fluid before treatment did not affect the incidence of reactions.[8]

The observations presented concerning two aspects of the febrile reaction in cases of neurosyphilis, i. e., the incidence and the pattern of fever, are at variance with those made in cases of early syphilis. Thus, approximately one half of the patients with early infectious syphilis had fever in response to penicillin, and this incidence was not related to the stage of infection. In contrast with this, 93 per cent of a selected group of patients with dementia paralytica and markedly abnormal cerebrospinal fluid showed reactions. Also, individual responses in patients with neurosyphilis followed a much more irregular temporal pattern than those in patients with early syphilis.

In neurosyphilis, as in early syphilis, the reaction is an all or none phenomenon. It occurs with equal incidence and severity with any dose of penicillin above a threshold level (10 to 20 units per kilogram). This dose is too small to destroy surface organisms in lesions in early syphilis. The reaction cannot be avoided by administration of penicillin in this small initial dose. In patients with neurosyphilis, as in those with early syphilis, multiple febrile responses may be produced by repeated small doses but not by repeated large doses.

An elucidation of the mechanism of the Herxheimer reaction in early syphilis and in neurosyphilis will require the unraveling of these many variables. The present clinical observations on patients with neurosyphilis point to the need for additional study, particularly of patients with dementia paralytica.

SUMMARY

1. Febrile Herxheimer reactions were observed in 34 per cent of 349 patients with various types of neurosyphilis treated with penicillin. Seventy-four per cent of patients with dementia paralytica had reactions. The incidence was significantly higher in patients with increased white blood cell counts, increased total protein contents and strongly positive reactions to complement fixation tests of the cerebrospinal fluid than in patients who had a normal cell count and a normal protein content in the fluid.

2. The incidence of the reactions in patients recently treated with metal chemotherapy was similar to that observed in previously untreated patients.

3. The temporal patterns of the febrile reactions in patients with neurosyphilis were variable. Maximal responses occurred over the wide range of four to twenty-four hours after the injection of penicillin.

8. Unpublished data.

Approximately 50 per cent of the patients had maximal elevations in temperature between twelve and sixteen hours after injection.

4. The incidence of febrile reactions after small initial doses of penicillin (20 units per kilogram) was approximately the same as that observed after the usual therapeutic doses (2,500 to 5,000 units per kilogram). With an extremely small dose (10 units per kilogram) of penicillin, reactions were not observed.

5. With repeated small doses of penicillin (20 units per kilogram), double and multiple reactions were produced in the same patients.

6. These observations demonstrate that febrile reactions in patients with neurosyphilis are not prevented by the administration of small initial doses of penicillin in the range of 20 units per kilogram of body weight.

News and Comment

GENERAL NEWS

United States Army Dedicates New Hospital.—Army officials announce the dedication of Tripler General Hospital, latest and finest addition to the medical facilities of the United States Army, at a formal ceremony held at the hospital on Moanalua Ridge, Honolulu, Hawaii, on Sept. 10, 1948.

The dedication day program, to which the public was invited, included an "open house" tour of the 1,500 bed structure. The ceremony was held in the hospital's flagpole area, which commands a sweeping view of Honolulu's ocean front from Diamond Head to Pearl Harbor and beyond. Here prominent civil and military officials gathered, with representatives of Hawaii's business and community life, formally to dedicate the hospital structure, which will afford vitally needed military facilities for adequate care of sick and convalescent patients under treatment in the Middle Pacific areas.

This Army hospital, which is capable of expansion in a critical emergency, normally will provide care for United States Army and Air Force personnel and their dependents, patients assigned by the Veterans Administration and patients submitted for entrance by the United States Public Health Service.

Tripler, which replaces the 147th General Hospital, long familiar to Honolulans as "Old Tripler," opposite Fort Shafter on King Street, is an Army post under command of Col. H. H. Twitchell, Medical Corps. The main hospital unit is a miniature city in itself, having, in addition to its comprehensive medical facilities, wards, dining rooms, kitchens, supply rooms, engineering plant and administrative offices, such other features as a radio station, post office, libraries, barber and beauty shops and post exchange.

In addition to the main hospital buildings, Tripler General Hospital includes nurses' quarters, enlisted men's barracks and mess, motor pool, warehouse and commissary, fire house, incinerator, gate house, utility shops, laundry and boiler house.

Work is authorized for the construction in the near future of a patients' recreation building, a gymnasium, athletic field, tennis courts and additional housing for personnel.

When completed, the hospital grounds will be landscaped as a great garden of tropical trees and shrubs, making Tripler General Hospital not only a medical asset of vast proportions to Hawaii, but also an attraction of scenic beauty.

National Gastroenterological Association Announces Its 1949 Award Contest.—The National Gastroenterological Association announces its annual cash prize award contest for 1949. One hundred dollars and a certificate of merit will be given for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The winning contribution will be

selected by a board of impartial judges, and the award is to be made at the annual convention banquet of the National Gastroenterological Association in October 1949.

Certificates awarded to other physicians will be mailed to them. The decision of the judges will be final. The association reserves the exclusive right of publishing the winning contribution, and those receiving certificates of merit, in its official publication, *The Review of Gastroenterology.*

All entries for the 1949 prize should be limited to 5,000 words, typewritten in English, prepared in manuscript form, submitted in five copies and accompanied with an entry letter. They must be received not later than April 1, 1949. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23.

International Congress on Rheumatic Diseases Announced.—The first International Congress on Rheumatic Diseases to be held in the United States will meet at the Waldorf Astoria in New York May 30 to June 3, 1949.

Seven scientific sessions are planned, as well as five one hour round table conferences on various clinical topics, under the leadership of authorities in the respective fields. Short clinics, papers and reports will be given concurrently at four or five New York hospitals during the three afternoons.

Instantaneous translations of the scientific papers will be made by means of the I. B. M. wireless system. The official languages of the congress will be English, French and Spanish.

The meeting will be an open one. Members of the International, the European and the Pan American Leagues against Rheumatism, as well as the Canadian Rheumatism Association, the British Empire Rheumatism Council, the Heberden Society of London and the ten state or city rheumatism societies affiliated with the American Rheumatism Association are especially invited.

PERSONAL NEWS

Dr. A. J. Carlson Given Honor Award of Mississippi Valley Medical Society.—Dr. A. J. Carlson, of Chicago, has received the Honor Award of the Mississippi Valley Medical Society for 1948, a gold medal and a certificate.

The "Honor Award" is a new award given by the society from time to time to those who have made distinguished contributions to clinical medicine. Dr. Carlson is the first recipient. He is the Frank P. Hixon Distinguished Service Professor Emeritus of Physiology at the University of Chicago and past president of the American Biological Society, the American Physiological Society, the American Association for the Advancement of Science, the American Association of University Professors, the Federation of American Societies for Experimental Biology and the Institute of Medicine of Chicago. He has long been known for his medical school teaching (since 1904), his research work and his contributions, which exceed 200 articles and books, in the fields of physiology and nutrition.

Dr. Louis H. Jorstad Given Distinguished Service Award of Mississippi Valley Medical Society.—Dr. Louis H. Jorstad, of St. Louis, has been honored by the Mississippi Valley Medical Society as the recipient of its Distinguished Service Award for 1948. The award consisted of a gold medal and a certificate.

Dr. Jorstad has given much of his time to postgraduate medical education and has served with distinction on the staffs of a number of well known St. Louis hospitals. For the past ten years he has been chairman of the Missouri State Chapter and the Greater St. Louis Chapter of the American Cancer Society and also an officer in the Mississippi Valley Medical Society.

Correspondence

PROTHROMBINOPENIC EFFECT OF PENICILLIN

To the Editor:—Because of the war in our country we lost contact for a time with the recent American medical publications, and it has been only lately that we received the back numbers of the ARCHIVES OF INTERNAL MEDICINE.

In the review on syphilis by F. W. Reynolds and J. E. Moore (ARCH. INT. MED. **81**:85 [Jan.] 1948) the action of penicillin on prothrombin in blood is mentioned. The authors quote reports from literature showing thrombopenic, as well as thromboplastic, effects of penicillin, without concluding which of these results is the correct one; but they add that there is no report of thrombotic accidents in medical practice after use of penicillin.

In this connection I should like to direct your attention to the article "Prothrombinopenic Effect of Penicillin in Men" (Lewitus, Z. A., and Aschireli, A.: Harefuah **35**:15 [July 15] 1948) in which we showed that in 94 per cent of our patients who received penicillin there was a definite decrease of the prothrombin activity in the blood to a level between 50 and 60 per cent of normal. The depression lasted during the entire time of penicillin medication, the prothrombin returning after interruption of medication to the previous levels. This decrease in prothrombin could be corrected by injections of vitamin K. We thought this effect of penicillin to be analogous to the one known to occur from the sulfonamide drugs.

The contradictions of the investigators regarding the effect of penicillin on the prothrombin seem largely influenced by the fact that in the first hours after penicillin medication a rise in prothrombin activity sometimes occurs, and the prothrombinopenic effect becomes evident only after elapse of three to four days.

We saw the practical implications of these facts in the combined penicillin-dicumarol therapy for infective thrombotic processes, in which we had to use much less dicumarol than is usually prescribed.

Z. A. LEWITUS, M.D., Affuleh, Israel.

Book Reviews

Lipoidtransport: Belyst ved studier over lipaemi i graviditet og lactationsperiode. By Mogens Ingerslev. Pp. 107. Copenhagen: Ejnar Munksgaards Forlag, 1942.

This monograph concerns studies on blood lipids in the cat and rabbit, in non-pregnant, pregnant and lactating animals, in an attempt to elucidate the question concerning the transport of fatty acids across the cell membrane. The transport of lipid through the placental membrane is considered as a paradigm of lipid transport through cell membranes in general.

From experiments performed, no decisive role could be attributed to the effect of the estrogenic hormone, the corpus luteum or the chorionic hormone on blood lipids. Hyperlipemia in pregnancy is considered a physiologic expedient and hypolipemia as due to difficulty experienced by some animals in meeting the increased demands which pregnancy makes on the fat exchange. Varying blood levels during lactation are considered to be related to differing degrees of activity of the mammary tissue.

From experiments on pregnant animals, evidence indicates that an active transport of lipid material occurs through the placenta in the last part of gestation. Fatty acids are transported through the placenta largely as neutral fat, to a lesser degree as phospholipids and only in minor amounts as cholesterol esters. No information could be obtained of the amount or form in which fatty acids are transported from the blood stream to the mammary gland.

Approved Laboratory Technic. By John A. Kolmer, M.D., PH.D., Sc.D., LL.D., F.A.C.P., and Fred Boerner, M.D. Fourth edition. Price, $10. Pp. 1,017. New York: D. Appleton-Century Co., Inc., 1945.

This textbook has enjoyed such general acceptance as an authority in its field for so many years that it is difficult for a reviewer to do more than call attention to a new edition.

As the editors point out, the present edition has been extensively revised and rewritten, in addition to which a considerable amount of new material has been added to encompass the newer methods for existing determinations where these represent an advantage in facility of performance and accuracy as well as a wealth of entirely new technics. The material is presented in a lucid manner, with an admirable degree of compromise between too little detail for the student and a burdensome amount for the expert. This text is confined in the main to technical procedures and normal values, the changes due to disease and their interpretation being considered in a separate book by Dr. Kolmer.

This has been found a useful reference work both in the laboratory and for teaching purposes.

Nuove vedute sulla malaria. By M. Ascoli, M.D. Pp. 211. Rome: Istituto Bibliografico Italiano, 1945.

This book is a collection of a series of lectures on malariology held at the University of Palermo in 1945 by Professor Ascoli and his associates.

Since 1936 Professor Ascoli has written widely on his concept of the malaria infection as a two phase process: a first (septicemic) phase, responsible for the acute episodes of the disease in which the parasites circulate and reproduce in

the blood stream, and a second (focal) phase, in which the parasites perpetuate the infection by remaining in the red blood cells stationed in the ordinary blood reservoir organs (especially the spleen). This situation would be responsible for the occurrence of relapses and for the bad condition of the patient between acute episodes. The first phase responds to chemotherapy; the second does not. However, intravenous injection of increasing amounts of epinephrine hydrochloride, from 1/100 to 1/10 mg., over a variable period (twenty to thirty days) exercises an important therapeutic action in the focal phase by preventing, to a large extent, further relapses and improving the general state of the patient. The mechanism of this therapeutic effect is probably mainly connected with the splenocontraction determined by the epinephrine as well as other factors, obscure at present.

The physiologic basis, clinical results, modifications induced in some biochemical findings and technic of the hormonal therapy are presented in the first part of the book. Of particular interest are new statistical data offered to show the drastic reduction in the number of relapses after hormonal therapy and its effect in extremely serious cases of pernicious malaria and other severe complications when administered in very high doses (1/10 Gm. twice a day) and when associated with quinine given parenterally. The second part of the book includes a heterogeneous series of lectures covering problems of epidemiology and transmission of the malarial infection. The possibility of the existence of an extraerythrocytic cycle of the malarial parasite (as suggested by Raffeale) is discussed with relation to its importance in the understanding of the malarial infection. Also of interest is a chapter showing ineffectual results in securing eradication of the disease at the chronic stage through protracted chemotherapy in the out seasonal period.

The book is intended principally to give current information to the general practitioner practicing in malarial areas. As such, it is of profitable and interesting reading. To the more experienced worker, however, the main interest of the book is in the well documented discussion of the epinephrine treatment of malaria which has received much undeserved criticism even in the country in which it was devised. From this point of view, the book is stimulating and useful for consultation.

Cardiopatias congenitas de la infancia. By Agustin Castellanos y Gonzalez, M.D. Price, $9. Pp. 406, with 59 illustrations. Habana: M. V. Fresneda, Publisher, 1947.

This work constitutes a textbook for a course on congenital heart disease given by the author at the University of Habana. It is primarily aimed, however, at the pediatrician rather than at the student, as the material is covered in a fairly exhaustive manner. The embryologic basis of cardiac anomalies is well reviewed, followed by a discussion of the methods of the investigation that apply to congenital heart disease. A discussion on cyanosis, including gasometric studies, is then presented and followed by a general description of the cyanotic syndromes. Detailed studies of the individual congenital cardiac abnormalities constitute the final section of the book.

Emphasis is primarily laid on diagnosis, prognosis and treatment, and particular attention is given to those congenital cardiac conditions that are amenable to surgical correction. Particularly impressive are the descriptions of roentgenographic and gasometric studies as they apply to the definitive diagnosis of cardiac anomalies. Many diagrams and a number of photographic reproductions

of angiograms are included for purposes of illustration of the diagnostic features involved.

This book is of great interest to anyone who desires to obtain information on cardioangiographic technics and interpretation, and having been one of the earliest workers in this particular field, Dr. Castellanos is well equipped to supply it. Many of the angiographic concepts discussed represent the author's original work, but abundant references are made to other investigators.

Kinesiology Handbook; A Study Guide and Laboratory Manual. By Gladys Scott, State University of Iowa. Price, $2. Pp. 148. New York: F. S. Crofts Company, 1947.

As has been pointed out by Dr. C. H. McCloy in the introduction to this handbook, "the concepts of mechanics have usually been taught with no relationship to the movements of man." The author has overcome this difficulty by assembling special experiments and problems which do apply to man. This text is "designed as a workbook and study aid for students of kinesiology." It includes twenty-one lessons on various phases of kinesiology, and in each lesson there is an introduction, a list of references, a list of equipment required for the lesson, a description of the project and finally a list of questions elucidating the facts learned from the lesson.

Such subjects as motion in relation to structure of joints, action of the muscles of the various parts of the body, muscular tonus, muscular fatigue, leverage, inertia, relaxation, locomotor skills, development of muscular strength and of muscular tonus and measurement of strength of groups of muscles are discussed. Professors of anatomy in our medical schools might well advocate greater consideration of this subject in teaching medical students because modern physicians should be well grounded in kinesiology and functional anatomy.

This handbook is well organized and well planned and should prove a useful teaching aid, not only for students of physical education, physical therapy and occupational therapy but also for medical students.

Psychobiology and Psychiatry: A Textbook of Normal and Abnormal Human Behavior. By Wendell Muncie, M.D. Second edition. Price, $9. Pp. 620. St. Louis: The C. V. Mosby Company, 1948.

The second edition of this book is disappointing in many ways, most particularly because it falls short of its purpose, which is to present an eclectic approach to and an explanation of the problems of psychiatry. Even so, it is the most complete textbook statement of the many important contributions made to psychiatry by Dr. Adolf Meyer and his students. The disappointments arise from omissions, condensations, misplaced emphasis and elaboration of details tangential to the truly pertinent data of psychiatry.

The contents constitute three rather distinct monographs. Part I, "Psychobiology—The Study of Normal Behavior," is presented in four chapters. It contains an outline of the Meyerian assessement of personality, and it is essentially a descriptive and an evaluative analysis of behavioristic phenomena. As an outline of a clinical inquiry into the resources of the total human personality, its growth, development and maturation, it is necessarily abbreviated and condensed. Although it subsumes the nodal points of a comprehensive discussion, it lacks the requisite definition for a student's textbook.

Part II, "Abnormal Behavior—Pathology and Psychiatry," in 14 chapters treats of the gamut of disorders which comprise the typical deviations from modal

behavior. These are organized in a form which covers the classic clinical features of each syndrome. They are illustrated by case presentations with graphic life charts including the therapeutic regimen which has been followed and contain a summary of comments.

Part III, "Treatment," consists of all chapters which describe the essentials of psychiatric treatment in a general fashion. Mention also is made of the specific technics which are useful in the management of the syndromes discussed in part II. However, the presentation in this part has been sacrificed to the first two parts. For example, insulin and electroshock therapy have been slighted. The discussion of prefrontal leukotomy is similarly condensed. The details of narcosis and use of barbiturates for interviews are sketchy. Too casual mention is made of the problems of alcoholism and drug addiction. The therapy for states of vitamin deficiency is superficial.

A disproportionate emphasis is given to the minutiae of examination. The orientation of medical students in the principles of dynamic psychiatry requires that they know more than the way in which to elicit or record descriptions of ideation, affect or behavior. The pages which are devoted to the superfluous outline of neurologic reflexology and to unelaborated listing of general, not particularly informative statements about the physical concomitants of mental disease could well have been used for this purpose.

On the other hand, the sections which are given to clinically descriptive psychiatry are complete for students' purposes. Each nosologic category is illustrated by a well chosen case study. If the author had synthesized and integrated the wealth of material he presents and related it to a more dynamic developmental background, he would have accomplished the goal of an eclectic orientation.

An Introduction to Gastro-Enterology. By James Dunlop Lickley, M.D. Price, $3. Pp. 143. Baltimore: The Williams & Wilkins Company, 1947.

This is an elementary manual intended for beginners who are interested in studying, in a résumé form, the anatomy and physiology of the digestive tract. It may prove of some assistance to physicians in their postgraduate courses. The last 50 pages of the book deal with some practical clinical applications. A correlation of physiologic facts with various signs and symptoms is made, but no attempt has been made to outline the treatment.

Las arritmias en clínica (diagnóstico, pronóstico y tratamiento). By Antonio Battro, M.D. Pp. 511, with 299 illustrations. Paper. Buenos Aires: "El Ateneo," 1948.

The title of this book does not do the work full justice. While the author deals adequately with cardiac arrhythmias, their diagnosis and treatment, he prefaces this with a discussion of the heart beat from the physiologic standpoint.

He deals well with the fundamentals of electrocardiography, including unipolar chest and limb leads, and other methods of registration, including heart sounds. This is something that other writers in this field might well imitate. He does not consider seriously electrocardiographic studies of conditions other than arrhythmias. But this is not his intention.

The discussion of arrhythmias covers well known forms and some less common ones such as the Wolff-Parkinson-White syndrome and ventricular fibrillation. Included, of course, are the blocks, both auriculoventricular and bundle branch blocks. There is also a short discussion of the use of esophageal leads.

Illustrations and diagrams, particularly those dealing with physiologic aspects and the tracings obtained by means of unipolar electrocardiograms, are particularly good.

One will find here an excellent discussion of all types of cardiac arrhythmias, together with an equally good bibliography in this field.

Medical Research in War. Report of the Medical Research Council for the Years 1939-45 by the Committee of Privy Council for Medical Research. Price, 7s. 6d. (approximately $1.75). Pp. 455. London: His Majesty's Stationery Office, 1948.

This impressive report of the Medical Research Council for the years 1939 to 1945 is the counterpart of the American "Advance in Military Medicine" recently published under the sponsorship of the Committee on Medical Research. The British report is of particular interest for the record since it enumerates the names of all concerned as well as abstracts of the work accomplished. One is amazed at the extent and the scope of the ground covered—a real tribute to the contributions of civilians to military medicine.

Arterial Hypertension: A Follow-Up Study of One Thousand Hypertonics. By Poul Bechgaard. Price, 8 kroner. Pp. 358. Copenhagen: Arnold Busck, 1946.

This 350 page paper-bound volume comprises a clinical and statistical evaluation of over 1,000 cases of arterial hypertension. These cases were observed by the author in the outpatient department of the Poli Clinic of the Rigshospital in Copenhagen. Original hypertensive clinical and laboratory studies were made between 1931 and 1938 on all patients with blood pressures of 180 systolic or 160 systolic and 100 diastolic, and repeated examinations were made four to eleven years later.

Few prolonged and detailed studies have previously been made on a large series of hypertensive patients. This study was undertaken in order to help establish a base line for a clinical classification, predominant symptoms, complicating diseases, age groups and prognosis in relation to untreated patients with hypertension. Such a basis of comparison is necessary in order to evaluate both modern and future methods of therapy of hypertensive disease.

The author has generously summarized the outstanding American literature on hypertensive vascular disease as it has referred to etiologic factors, morbid classification, clinical evidence and causes of death. He has emphasized renal complications as they reveal themselves during the course of hypertension. His findings in this group of patients reveal that malignant nephrosclerosis occurs in approximately 1 per cent of all patients with hypertension.

As the cause of death, heart disease ranks first in 45 per cent of the patients, apoplexy second in 16 per cent of the patients and renal insufficiency third in 10 per cent of the patients. All in all, his investigation revealed a rather good prognosis for hypertension. In men the total mortality rate was found to be 288 per cent and in women 143 per cent when the mortality ratio of 100 per cent in the Danish population was used. The prognosis is particularly good in women who have noncomplicated hypertension with diastolic pressures below 130 mg. The mortality figures are only slightly higher than those for the general population.

Although these studies are not particularly revealing, they do represent a detailed piece of clinical investigation extending over a long period. The statistical material is well presented and is of interest to the student of hypertensive vascular disease.

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